



# MEDICINE

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# THE PARATHYROID GLANDS<sup>1</sup>

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## GROSS ANATOMY OF THE PARATHYROID GLANDS

The parathyroid glands in the human subject are bean-shaped structures 3 to 15 mm long, and 2 to 3 mm broad and thick. They are yellowish-brown to brown-red in color. As a general rule there are four distinct glands, situated in such relation to the thyroid lobes that it has been customary to distinguish between a superior and an inferior pair of glandules. The superior pair are the more constant in position. They occur on the medial aspect of the dorsal surface of each lateral lobe of the thyroid gland at about the junction of its upper and middle thirds. The inferior pair occur also as a rule on the dorsal surface of each lateral lobe of the thyroid gland but further caudad. Accessory parathyroids are sometimes present and these may be situated in the thorax nearer to or embedded in the thymus gland (Cowdry).

Parathyroid glands have been recognized in all classes of the vertebrates with the exception of the fishes (Cowdry).

The anatomical arrangement of these glands in certain of the mammals is a matter of considerable interest and affords an explanation for some of the contradictory results reported by some of the earlier workers in this field. In the dog and cat for example, the four glandules are so closely associated with the lobes of the thyroid that in the operation for thyroidectomy, they are completely removed whereas in the rabbit, removal of the thyroid gland results in only one pair of parathyroid glandules being taken away. The superior pair of glandules are frequently described as "external" and the inferior pair as "internal" in certain of the mammals, thus indicating that one pair of glandules are more or less removed from the thyroid lobes and that

<sup>1</sup> Lecture delivered before the Harvey Society in New York City on January 2, 1926

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one pair are imbedded in the lobular tissue of the thyroid. Accessory parathyroids are also very common in certain of the lower mammals.

#### MINUTE ANATOMY AND EMBRYOLOGICAL DEVELOPMENT OF THE PARATHYROID GLANDS

The parathyroid gland possesses a capsule of fibrous connective tissue. The glandular cells within the capsule are disposed in columns or clumps, which are separated to a greater or lesser extent by bands of connective tissue which are continuous with the capsule. Two types of glandular cells are usually recognized. The parenchyma consists in the main of the so-called chief cells of large polygonal type which are characterized by their clear cytoplasm and faintly staining nuclei. The second type known as the oxyphil cells, stain strongly with eosin and the nucleus with hematoxylin.

The parathyroid glands develop as thickenings of the endoderm of the third and fourth branchial clefts. The superior pair of glandules are related to the fourth branchial clefts developmentally while the inferior pair are similarly related to the third branchial clefts.

#### DISCOVERY OF THE PARATHYROID GLANDS

The superior pair of parathyroid glands was first described by Sandstrom in 1880. He found these bodies constant in fifty autopsies in man and he also studied and accurately described their position and structure in the dog, cat, rabbit, ox and horse. Sandstrom's important contribution was lost sight of and it was not until eleven years later when Gley rediscovered the superior pair of parathyroid glands that due attention was called to these small structures.

Kohn (1895) discovered the inferior or internal pair of parathyroid glands. This author recognized that every animal is provided with four parathyroid glands occurring in two pairs. An internal pair present in the substance of the thyroid and an external pair, situated at some distance from the thyroid in the herbivora, but in the carnivora lying on the surface of that gland and usually within its capsule. Kohn insisted that the parathyroid glands are organs anatomically separate and functionally distinct from the thyroid. In this he differed from Gley who held at first that the parathyroid glandules represented embryonic thyroid tissue.

## PHYSIOLOGY OF THE PARATHYROID GLANDS

*Historical*

The earliest recorded experiments on animals bearing upon the physiology of the parathyroid glands are those of Raynard (1835) Raynard removed the thyroid gland from a number of dogs and found that death frequently resulted in the course of a few days

Schiff (1859) removed the thyroid gland from a number of animals of different species—rabbits, rats, dogs, guinea pigs and fowls and found that while some survived, others died within a few days In 1884 he published the results of a more extensive investigation He states in this communication that no symptoms followed removal of the thyroid gland in the case of rats and rabbits whereas in the dog and cat, the result was almost invariably fatal

When Gley (1891) later discovered the external pair of parathyroid glands, it became apparent to him that thyroidectomy as previously practiced meant in the case of the dog and cat parathyroidectomy as well, and the divergent results obtained by Schiff following thyroidectomy in different species of animals came to have a rational explanation Gley carried out a series of experiments the results of which demonstrated that the acute symptoms manifested by certain animals following thyroidectomy are due to removal of the parathyroid glands along with the thyroid Vassale and Generali (1900) removed the four parathyroids from ten cats and nine dogs, leaving the thyroid gland almost intact Of the cats so treated nine died within ten days, the majority dying about the fifth day All of these presented a typical syndrome, viz, fibrillary contractions and muscular spasms, psychical depression, rigid and uncertain gait, anorexia, tachycardia, rapid emaciation, fall in body temperature and death Of the nine dogs in this series all died within eight days, most perishing on the third or fourth day All were in good condition on the day following the operation Symptoms began to appear on the second or third day and death resulted shortly thereafter The symptoms recorded were tremors, psychical depression, paresis of the muscles of mastication, trismus, rigidity of the hind limbs, uncertain and spastic gait, muscular weakness and convulsions There was loss of appetite and vomiting, palpitation and dyspnea, the urine was scanty and some-

times showed traces of albumin. At post-mortem examination, slight congestion of liver and kidneys was noted but nothing specific to point to the cause of death was found. They adopted the view that the parathyroid glands exercise normally an anti-toxic function and that their removal causes death by poisoning. Since the work of Vassale and Generali, numerous investigators have demonstrated the vital nature of the parathyroid glands. The recent work of Nicholas and Swingle (1925) on cats would seem to establish conclusively that complete removal of the parathyroid glands is a direct cause of a specific syndrome of symptoms and death.

Apart from this one fully demonstrated fact that the parathyroid glands are vital structures, the physiology of these glands has been quite obscure. There have been two main theories of parathyroid function and each of these has had its adherents. These theories will now be discussed briefly.

#### THE TOXIN THEORY

As has been already stated Vassale and Generali (1900) attempted to explain the cause of parathyroid tetany by assigning an anti-toxic function to the parathyroid glands. They held, the thyroid gland, stimulated metabolism. The more intense the metabolism, the more toxic substance would be produced. In this manner they fitted a number of outstanding experimental observations to their theory. Among these latter observations were the following. Parathyroidectomy is less serious and runs a milder course in old than in young dogs. It is extremely severe in dogs that eat heavily, particularly of meat, and in fasting animals the symptoms are much less severe.

Many attempts were later made to demonstrate the hypothetical tetany toxin in the blood of parathyroidectomized animals. None of these attempts have been attended with clear cut results. Biedl and others have reported that copious bleeding and the transfusion of normal blood relieves the symptoms of tetany in parathyroidectomized animals. It is argued from these results that a toxin present in the blood is responsible for the symptoms and by the process of blood-letting the organism may be temporarily freed from the effects of the poison.

MacCallum (1909) observed that the withdrawal of approximately

one-third of the blood from an animal in the acute stage of parathyroid tetany and the replacement of the same with normal saline solution caused the symptoms to be promptly relieved. This was confirmed by Berkeley and Beebe (1909). These latter investigators believed that parathyroid tetany is due to a toxic product of metabolism derived from the decomposition of albumin. The fact that the symptoms are considerably aggravated in meat fed dogs confirmed them in this belief. Joseph and Meltzer (1911) showed that the injection of sodium chloride solution without previous bleeding will allay the neuromuscular symptoms. Koch (1912) and (1913) described the presence of methyl-guanidine and other bases in the urine following parathyroidectomy.

Paton and his collaborators later claimed to establish the following points

- 1 That the symptoms produced by guanidine and methyl-guanidine are identical with those seen in operative and idiopathic tetany

- 2 That very small doses of these substances markedly aggravate the symptoms of tetania parathyreopriva

- 3 That their amount in the blood and urine is increased in experimental tetany and in the urine in idiopathic tetany

Findlay and Sharpe (1920), and Natrass and Sharpe (1921) have observed an increased amount of guanidine, apparently as di-methyl-guanidine in the urine in cases of tetany in adults. Paton (1924) states that the mass of evidence indicates that complete removal of the parathyroid tissue leads to a fatal toxemia, he further hypothecates that the parathyroids through their internal secretion control the tone of muscles by regulating metabolism, i.e., the production and destruction of guanidine in the body. The views of the Glasgow school have received support from the work of Frank, Stern and Notthmann, Gyorgy and Vollmer, Palladin and Griliche and others.

It must be admitted that a very strong case has been made out for the guanidine intoxication theory of parathyroid tetany. The evidence, however, consists so largely of the circumstantial type that it fails to carry with it the weight of final conviction.

#### THE CALCIUM THEORY

J. Loeb (1901) showed that the injection of any salt that precipitates calcium causes muscular twitchings.

MacCallum and Voegtlin (1909) demonstrated in the condition of parathyroid tetany, a lowered calcium content of the tissues and body fluids, especially of the blood, the calcium content of which might be reduced to as much as 50 per cent of its normal value. They also showed that calcium salts injected intravenously caused the convulsions of tetany to cease and the animal to be restored to a normal condition. Oral and subcutaneous administration of calcium salts had a similar effect although the beneficial action developed much more slowly. They concluded that the function of the parathyroid glands is to regulate the calcium exchange in the body and considered that all the symptoms following parathyroidectomy are due to calcium deficiency.

MacCallum (1912) showed that the galvanic hyperexcitability of the nerves which is a characteristic feature of tetany is due to some change induced in the blood by parathyroidectomy. By causing the blood from a tetany dog to flow through the leg vessels of a normal dog he demonstrated that an excitability identical with that found during tetany appears in the nerves of the normal leg.

Later MacCallum, Lambert and Vogel (1914) showed quite conclusively by means of dialysis experiments that the change in electrical excitability of nerves in the tetany state is due to diminished calcium in the blood.

Luckhardt and Goldberg (1923) showed that parathyroidectomized dogs can be kept free from symptoms and in good health even on a meat diet when calcium therapy is pushed far enough.

Salveson (1923) obtained somewhat similar results and related the whole symptomatology of parathyroid deficiency to a lowered calcium content of the blood. The calcium content of the blood he held is normally controlled by the parathyroid glands.

Collip (1925) reported results in accord with these latter authors.

Clinically the immediate relief of symptoms following the intravenous administration of calcium salts in low blood calcium tetany, has been repeatedly confirmed.

MISCELLANEOUS OBSERVATIONS BEARING UPON THE PHYSIOLOGY OF  
THE PARATHYROID GLANDS*Acid-base equilibrium*

Wilson and his co-workers (1915) considered that deranged metabolism whereby the normal equilibrium between acids and bases in the blood is disturbed, is the cause of the symptoms of parathyroid tetany. They made a careful study of the ammonia excretion in parathyroidectomized dogs and found that the ammonia output is diminished at first but later increases when the convulsions start. Since the excretion of ammonia is dependent on the amount of acid which has to be excreted by the kidney, these authors concluded that a condition of alkalosis develops following the removal of the parathyroid glands. This condition they held is relieved by the development of a state of acidosis caused by acid formation during the convulsions. In confirmation of this, actual changes in blood reaction were demonstrated in the pretetany and tetany states.

Collip and Backus, and Grant and Goldman (1920) demonstrated that by voluntary hyperpnea, a state of tetany is produced. Forced ventilation of the lungs produces a state of alkalosis and in this condition, however produced, symptoms of tetany may be manifested. As the blood calcium may be perfectly normal in the tetany of alkalosis, it may be assumed that the symptoms result from a decrease in calcium ions which is an inevitable result of an increased pH of the blood.

Tetanic seizures have been produced by the disturbance in the lation equilibrium of blood or spinal fluid as by the injection of sodium chloride (Collip (1920) and Greenwald (1922)). It is doubtful if this type of experimental tetany bears any relationship to parathyroid tetany. The tetany of alkalosis does however bear a very direct relationship to parathyroid tetany. The administration of acids has been shown to have a definite beneficial effect in parathyroid tetany. This action of acids may be due to an increase in the ionization of the blood calcium resultant on their use. It has been our experience that, in about 50 per cent of untreated parathyroidectomized dogs, the outstanding prodromal sign of an approaching tetanic seizure is violent hyperpnea. The animals in this group and manifesting this



sign, are subject to tetanic seizures of the most violent sort and death results as a rule earlier than in the other group. Cameron and Carmichael (1925) report somewhat similar results. From these findings, it may be concluded that alkalosis may play a definite rôle in parathyroid tetany but it is not a necessary concomitant. When it is present the symptoms are exaggerated and early death is more likely to occur.

### *The intestinal factor*

Much evidence has been brought forward to show that both diet and the type of flora of the alimentary canal play a very important rôle in relation to the development of tetany in parathyroidectomized animals. Thus it has long been known that a meat diet precipitates the onset of symptoms and increases their severity while a milk diet decreases the severity or prevents the development of symptoms. Dragstedt and Peacock (1923) obtained results which indicated to them that the symptoms of parathyroid tetany are primarily the result of the absorption of the products of bacterial decomposition of meat in the intestine due to the development of a special proteolytic flora as a result of a meat diet. Their experiments also indicate, as have those of others, that tetany is much less marked when animals are given a milk diet. They also found that lactose and dextrin seem to have a special action in delaying the onset of symptoms. This action they have ascribed to the establishment by these food stuffs, of an aciduric flora in the intestine which prevents the bacterial decomposition of proteins into toxic split products.

Luckhardt and Compere (1924) have pointed out that changes in the permeability of the mucosa of the gut may have an important bearing in relation to parathyroid tetany.

That the liver plays an essential rôle in the development of the so-called toxemia of parathyroidectomized dogs has been argued by Blumenstock and Ickstadt (1924). These authors found that parathyroidectomy in Eck fistula dogs resulted in a delay in the appearance and a diminution in the severity of the characteristic symptoms. When symptoms did appear they were abolished with the greatest ease by the administration of calcium salts per os. They suggest that substances absorbed from the gut are not the direct toxic agents as such, but they may cause tetany after being modified by some tissues, most probably the liver.

*The beneficial effect of intravenous saline*

The fact that bleeding\* and the transfusion of normal blood is highly beneficial in parathyroid tetany coupled with the observation that intravenous injections of normal saline have a similar good effect, have done much in the past to discredit the calcium deficiency theory of tetany. Luckhardt and Rosenbloom (1921) made the case against the calcium theory much stronger when they showed that timely intravenous injection of calcium free Ringer solution prevents or controls tetany in parathyroidectomized dogs over a considerable period of time. With such treatment the calcium content of the blood must be still further diminished and yet the effect is beneficial.

*The blood chemistry in parathyroid tetany*

The most constant finding in the blood condition in parathyroid tetany is a greatly diminished calcium content.

Nearly all investigators agree that in the course of tetany there is a retention of phosphorus in the blood (Greenwald, Elias and Weiss, Elias and Spiegel). Greenwald has emphasized that the decrease in phosphorus excretion and the increase in blood phosphorus are out of proportion one to the other. He finds a considerable decrease in the excretion of phosphorus in parathyroidectomized dogs but only a slight increase in the inorganic phosphorus of the blood, a fact pointing to retention of phosphorus elsewhere than in the blood.

Underhill and Blaterwick (1914) observed hypoglycemia in dogs following parathyroidectomy. Salveson (1923) failed to confirm this. Our own results are in accord with Salveson in this matter.

Togawa (1920) found a condition of acidosis in dogs suffering from parathyroid tetany and also noted that the non-protein nitrogen of the serum is usually increased. Little importance can be attached to these latter results since the average control non-protein nitrogen value reported is 77 mgm per 100 cc of serum.

\* Swingle and Wenner (Amer J Physiol, lxxv, 372) have just reported that the withdrawal of considerable quantities of blood from dogs suffering from tetania parathyropriva promptly relieves the symptoms and induces a marked rise in the level of serum calcium. They state that the abatement of symptoms coincides with the rise in calcium and that within 10 or 12 hours after bleeding the calcium again decreases in the blood and tetany again appears.

Paton and his co-workers (1924) find an increase in methyl-guanidine in the blood

Greenwald (1924) was unable to demonstrate any toxin in the blood of parathyroidectomized dogs and is of the opinion that no toxin exists

Kramer, Tisdall and Howland (1921) found in infantile tetany that the inorganic phosphorus shows marked variation. They found that the concentration of sodium and magnesium is essentially normal while potassium is slightly increased. Calcium is lowered and is the one inorganic constituent of tetany blood, the concentration of which is markedly changed.

#### EXPERIMENTAL TETANY

Tetany has been produced in animals by various experimental measures. As the study of experimental tetany induced by means other than parathyroidectomy may throw some light on parathyroid tetany itself a number of the experimental tetanies will be briefly referred to

1. Any salt which will precipitate calcium in the tissues and body fluids causes muscular twitchings (Loeb (1901))

2. Sodium chloride given in massive doses by intravenous injection will produce tetanic seizures (Greenwald)

3. The intravenous injection of sodium bicarbonate has been observed on occasion to cause tetanic convulsions in both man and experimental animals (Tileston, Harrop, and others)

4. Morris (1922) has demonstrated that all conditions of anoxemia markedly increase the electrical excitability of nerve endings

5. Campbell (1925) has very recently suggested that tetany and convulsions are caused by oxygen deficiency in the cell (brain, spinal cord) and that the purpose of tetany and convulsions is to counteract this defect

6. Guanidine and methyl-guanidine produce a state of tetany somewhat similar to that seen in parathyroid deficiency. The action of these bases is cumulative (Paton)

7. Forced ventilation of the lungs is productive of mild tetany (Collip and Backus (1920), Grant and Goldman (1920)).

8. Gastric tetany has been produced in dogs by McCann (1918)

9 Binger (1917) showed that the injection of phosphates in sufficient amount would cause a decrease in the calcium content of the blood and produce tetany provided neutral or alkaline solutions were used. Acid sodium phosphate caused a decrease in the blood calcium but did not produce tetany.

10 Cameron and Carmichael observed tetany in a certain percentage of rats which had been fed desiccated thyroid gland.

11 Tetany can be produced in rats by dietary measures alone (low calcium and high phosphorus).

12 Tetany is manifested in rachitic rats.

13 There are at least three factors which influence the production of experimental tetany, viz., tissue anoxemia, disturbance in ionic equilibrium and pH.

#### TETANY AS A CLINICAL ENTITY

Tetany is a clinical syndrome characterized by a peculiar hyperexcitability of the nervous system (motor, sensory and autonomic) and in manifest cases, also, by spontaneous attacks of peculiar tonic spasms, involving certain groups of muscles or even the whole body musculature.

The syndrome can be easily and surely recognized, in all cases by demonstrating the existence of its most constant and characteristic mark, namely, an increased response to galvanization of the motor nerves (Erb's sign) (Barker).

Certain signs are usually present. Most important of these are the Trousseau and Chvostek phenomena. Pressure on the nerves in the bicipital sulcus gives rise to a peculiar obstetrical attitude of the hand and forearm (Trousseau). Tapping the facial nerve causes contractions of the muscles on the corresponding side of the face (Chvostek). Carpo pedal spasm is usually present in manifest tetany.

#### TYPES OF TETANY

##### *Infantile tetany*

This condition is most commonly seen in the so called tetany months of March and April.

Post-operative tetany or *tetania strumipriva* occurs as a result of

removal of or damage to (cutting off of blood supply) the parathyroid glands

Both infantile tetany and post-operative tetany are probably conditions similar to parathyroid tetany in animals. Both show a lowered calcium content of the blood and both types yield to calcium therapy.

### *Gastric tetany*

This condition was first described by Kussmaul. The blood calcium is normal in this type of tetany and the underlying causative factor would appear to be an alkalosis set up as a result of the withdrawal from the body of excessive amounts of acid.

### *Tetany due to hyperpnea*

Tetany due to excessive pulmonary ventilation has been reported (Barker and Sprunt (1925))

Other forms of tetany in the adult human subject are tetania gravidarum and idiopathic tetany.

### PARATHYROID GRAFTS

There are a number of cases of successful parathyroid grafts recorded in the literature. Schiff (1884) succeeded in keeping a thyroidless dog alive by the abdominal implantation of fresh thyroid glands. Eiselsberg (1892) showed more positively that the thyroid gland when implanted into the abdominal fascia or in the peritoneum of cats, healed in and prevented the occurrence of tetany. When the healed-in-tissue was removed tetany followed and the animal died.

Halsted (1909) has described the successful transplantation in dogs of both their own parathyroid glands and those of other dogs.

Successful transplantations of human parathyroid glands have been reported by a number of workers.

Borcher (1919) states that a single parathyroid gland is adequate to obviate symptoms in the human subject.

### PARATHYROID EXTRACTS

Moussu (1898) claimed to have arrested post-operative tetany in dogs by subcutaneous and intravenous injections of extracts prepared

from the parathyroid glands of the horse. He used sterile water and glycerin to prepare his extracts.

Vassale (1905) introduced an extract of parathyroid glands which he called parathyroidin. He asserted that it had a favorable effect upon tetany attacks in human beings. His method of preparing the extract was not published.

Vincent and co-workers (1905) were unable to prevent the onset of symptoms in thyroparathyroidectomized animals either by the use of thyroid or parathyroid gland extracts.

Berkeley and Beebe (1909) prepared an extract from beef parathyroid glands by the use of acetic acid, from which they separated a nucleoprotein. This parathyroid nucleoprotein they found to have curative properties when administered to parathyroidectomized dogs.

Berman (1924) published a short note in which he claimed to have isolated by acid alcoholic extraction of parathyroid glands a crystalline substance which raised the blood calcium when injected into rabbits.

MacCallum (1924) in a paper dealing with the pathogenesis of tetany refers to the use of parathyroid gland preparations as follows:

Extracts of parathyroid glands have naturally been tried, both experimentally and clinically, throughout many years and some of them seem to have some effect in restoring calcium balance and the normal excitability of nerves, but at best it is a slight and questionable effect and less satisfactory in experimental animals than in the tetany of adults, from which it may probably be assumed that the psychic effect of any treatment plays a part there.

Hanson (1923-1924) has published a series of papers in which he describes the preparation and use in both experimental animals and man of a weak hydrochloric acid extract of ox-parathyroid glands. He prepared the extract by first extracting the glands with boiling, dilute hydrochloric acid. Many of Hanson's results are highly suggestive of the presence of an active principle in his extract. No absolute scientific proof, however, is given of the presence of the parathyroid hormone in these extracts.

Collip (1924) brought forward final proof that extracts prepared by weak acid hydrolysis of the fresh or acetone preserved parathyroid glands of the ox contain the active principle of these glands. Thus

proof consisted in the demonstration that such extracts consistently and uniformly prevent or relieve tetany in thyroparathyroidectomized dogs. This result was obtained in the case of young dogs kept on a lean meat diet, and treated with alkalinized extracts. It was also shown that the probable manner of action of the hormone contained in these extracts is through a direct effect on calcium metabolism. The blood serum calcium of parathyroidectomized dogs is found to be elevated following the use of the extract. The injection of the extract into normal animals causes the blood serum calcium value to be elevated and a method of assay was later (Collip and Clark (1925)) developed based upon this finding.

These results have been confirmed by a number of workers, Macleod and Taylor, Cameron and Moorehouse, Greenwald,<sup>3</sup> Fisher and Larson, and Hjort.

#### PREPARATION OF THE HORMONE

Fresh glands are ground in a meat chopper, placed in large Pyrex tubes (5 + 45 cm) and covered with an equal volume of 5 per cent hydrochloric acid. Three per cent hydrochloric acid is used if the glands have been preserved in dry acetone. The tubes and their contents are then placed in a boiling water bath for from thirty minutes to one hour. During the digestion the mass is stirred and broken up with a glass rod until most of the material is in solution, and that which is not, quite finely divided. When this treatment is finished, the extract is diluted with four parts of hot water and set aside to cool. The fat, which separates and rises to the top of the container, congeals upon cooling and is removed mechanically. The liquid is thereupon made alkaline (pH 8.0 to 9.0) with sodium hydroxide which dissolves practically all the suspended material. Hydrochloric acid is then added with constant stirring until considerable precipitation occurs which, at the same time, permits rapid filtration. The object to be attained here is to have the liquid at a hydrogen ion concentration such that as much as possible of the active material is in solution, but at the same time rapid filtration is possible. Usually the hydrogen ion concentration is in the neighborhood of pH 5.5 to 5.6, but the

<sup>3</sup> Personal communication

proper condition can best be determined by trial. After the liquid is filtered the precipitate remaining on the filter is dissolved in weak alkali and again treated with hydrochloric acid as before. This process is repeated as long as any active material remains in the filtrates. This point is determined by noting whether upon making the filtrate acid to congo red and saturating it with sodium chloride an appreciable amount of precipitate is formed. The active substance is separated from the filtrates by salting-out with sodium chloride, the first filtrate being worked up separately from the subsequent ones. The salting-out is done by making the solutions acid to congo red and saturating them with sodium chloride. The substance generally flocks out and rises to the top of the liquid. The precipitate is transferred to a filter, separated from its mother liquor, dissolved in weak sodium hydroxide, centrifuged, and the liquid adjusted to pH 4.8. The isoelectric precipitate which thus separates is either filtered or centrifuged off, dissolved by the addition of hydrochloric acid, and the process repeated until the mother liquors are quite clear and devoid of color. The substance is dissolved in hydrochloric acid at pH of about 3, Berkefelded, standardized, and is then ready for use.

A very satisfactory preparation for laboratory use can be made from the original residue. Even after several extractions of this residue as above described, considerable of the active principle remains behind. This was at first overlooked since the washings which were found to be inert were made at a pH near to the isoelectric point. The residue has been worked up as follows. It is taken into solution by the addition of acid, sodium chloride is then added until flocculation occurs. The precipitate is removed and is then submitted to a process similar to that described.

#### THE CHEMISTRY OF THE ACTIVE EXTRACT

The chemical properties of the most highly purified active extract of the parathyroid glands of oxen which has been obtained are such as to indicate that it consists essentially of a protein-like substance. It gives the common protein reactions, namely, the xanthoproteic, Millon's, biuret, ninhydrin and Hopkins-Cole reactions. The Molisch carbohydrate reaction and the orcinol-hydrochloric test for pentose are not given. Sulphur and iron are present (Collip and Clark).



There is the possibility which cannot be overlooked that the active principle may be some fairly simple compound which associates itself with the particular protein-like fraction which has been dealt with. The fact, however, that proteolytic enzymes completely inactivate the most potent preparations argues against this possibility. It has also been found that no appreciable change in chemical composition or in physiological activity occurs when repeated isoelectric precipitation of already purified material is carried out. Thus in one experiment, material was purified by two precipitations with sodium chloride and ten isoelectric fractionations. The solid was washed with water at pH 4.8 and recovered by centrifuging. It was then suspended in absolute alcohol of such amount that the resulting concentration of the latter substance was 95 per cent. An equal volume of dry ether was added to the alcoholic suspension and the precipitate was recovered by centrifuging. The solid as obtained was washed with dry ether and finally the ether was removed and the substance was thoroughly air dried. On analysis, the air dried powder contained 14.5 per cent of nitrogen. Similar material which had been dried in vacuo over sulphuric acid and potassium hydroxide contained 15.5 per cent of nitrogen thus indicating that the purified powder is hygroscopic. The purified solid prepared as outlined above, was taken into solution in weak acid and precipitated isoelectrically. This process was thrice repeated. The precipitate was then treated with alcohol and ether as in the first instance. The air dried resultant solid contained 14.6 per cent of nitrogen and when submitted to the physiological test for potency showed no appreciable change (Collip and Clark).

The purified material in the form of the desiccated solid or in weak acid solution (sterile) has been found to be stable. The purified solid is soluble in absolute alcohol to the extent of 0.1 per cent. It is insoluble in acetone, ether and pyridine. Its physiological activity is completely destroyed by boiling for one hour with 10 per cent hydrochloric acid or 5 per cent sodium hydroxide. It is rendered inert by the action of both pepsin and trypsin. In order to be assured that the action of these four reagents was to effect complete destruction of the physiologically active material, a number of dogs were injected at frequent intervals over a period of many days with massive doses of this highly potent extract. This extract, divided into four lots, had

been treated respectively with 10 per cent hydrochloric acid, 5 per cent sodium hydroxide, pepsin and trypsin. Frequent blood serum calcium determinations were made and in no instance was any evidence obtained of the presence of the active principle in any of the treated extracts.

The active principle does not dialyze through collodion membranes to any appreciable extent.

It is removed from solution by Norit and by the Folin-Wu tungstic acid reagent.

Chemically the purified solid resembles insulin somewhat. Attempts to further purify it by the method recently employed so successfully in the case of insulin by Abel and his co-workers have not met with success in our hands. That it will ultimately be purified to a much greater extent would seem, however, an inevitable conclusion.

#### THE PHYSIOLOGICAL PROPERTIES OF THE ACTIVE PRINCIPLE

The outstanding physiological property of the active principle of the parathyroid glands is its specific effect on the concentration of calcium in the blood. There may be other direct effects of the active principle but this is the only one which has been absolutely proven. It is possible that all other effects resultant on the experimental production of hyperparathyroidism by means of the hormone, are purely secondary to the changes directly induced in calcium metabolism. Changes which occur in the last few hours of life in a dog for example which is in an essentially moribund condition as a result of parathyroid hormone overdosage, should not be interpreted as direct or immediate effects of the hormone. They are rather preterminal phenomena which have little practical bearing on the purely physiological effect of the hormone itself. The physiological action of the parathyroid hormone is normally to regulate calcium metabolism and to maintain a definite level of calcium in the circulating blood.

#### THE EFFECT OF THE INJECTION OF THE PARATHYROID HORMONE

##### *Normal animals*

There is an enormous variation in the response of different normal animals to injections of the parathyroid hormone. Single small

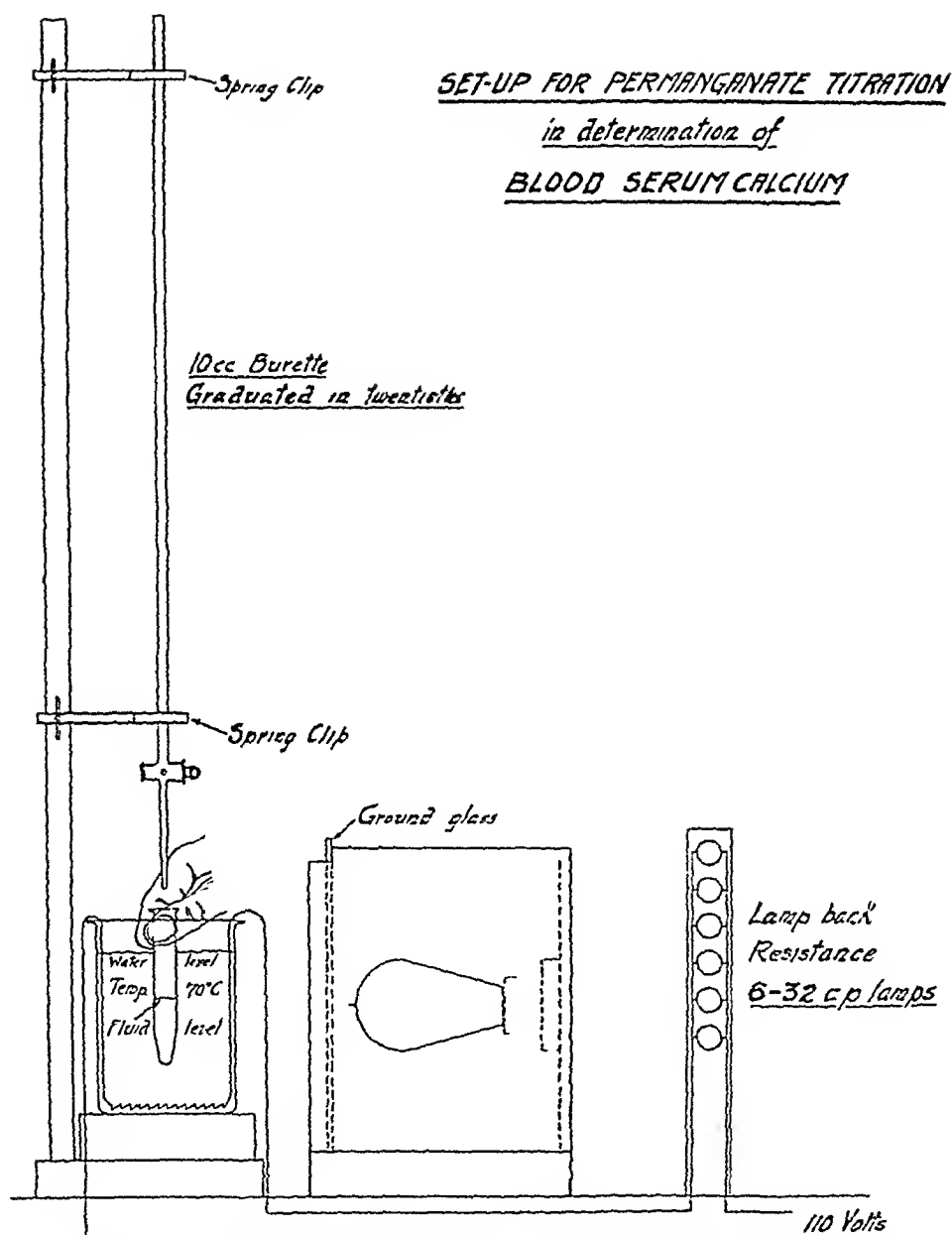


FIG. 1 SET-UP AS USED FOR PERMANGANATE TITRATION IN ESTIMATION OF BLOOD SERUM CALCIUM

doses have produced no objective effects in those animals so treated. The response to repeated injections at short intervals of time is much different. Some animals exhibit a typical train of symptoms which end fatally if the injections are continued past a certain point while others are relatively immune. Considerable work still remains to be done in this field. It would appear that the dog is of all animals the most susceptible to "poisoning" by overdosage. The cat responds in a somewhat similar manner but this animal is relatively slightly more resistant to the active extract than are dogs. Rabbits are practically

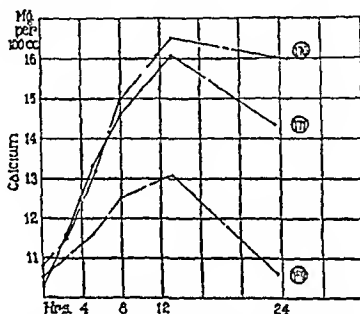


CHART 1 Showing that the response to single subcutaneous injections of parathyroid hormone is of a quantitative nature

Dog 169—22 kilos—received 50 units

Dog 171—20 kilos—received 75 units

Dog 170—19 kilos—received 100 units

immune to repeated injections of the hormone. Hens are in the same category.

The dog is the most suitable animal upon which to study the changes produced in blood chemistry following injections of the hormone. This is so for two reasons, viz., the nature of the response of this animal and the ease with which frequent blood examinations can be made.

It has been found that the main effect of single injections of active extracts of the parathyroid glands into normal dogs is an increase in the blood serum calcium value. For some hours following an injection the blood serum calcium gradually increases until a peak point is reached, a return to normal is then gradually accomplished. The

slope of the descending curve is somewhat the same as that of the ascending one. The peak point is reached in twelve to twenty-four hours after the injection but it is usually attained in from fifteen to eighteen hours.

It has been shown that the increase in blood serum calcium attained in fifteen hours is almost directly proportional to the dose administered. Thus, by using a large number of dogs and noting the blood serum calcium increases over the fifteen hours following the injections any given batch of extract can be physiologically standardized. Considerable variation is of course found in the response of different

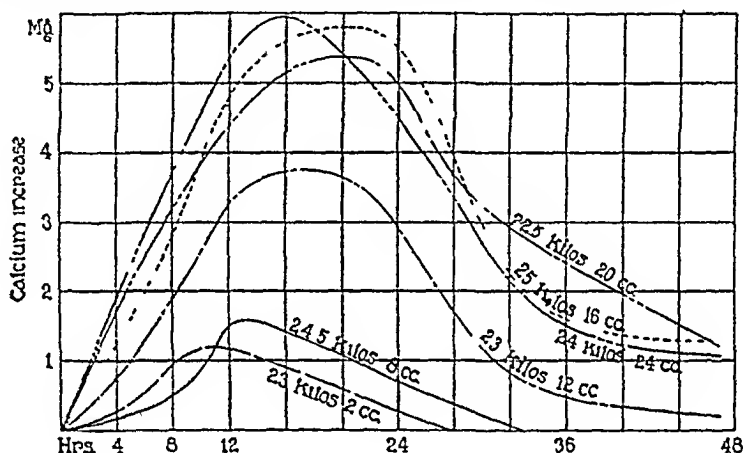


CHART 2 Constructed curves illustrating that the blood serum calcium response to a single injection is directly related to the size of the dose administered

dogs but by using a large number of animals in a potency test these variations are compensated for to a fair degree. No absolute relationship between the weight of an animal and the blood serum calcium mobilizing effect manifested has been found. For this reason, in potency testing, animals approximating to twenty kilos in weight are used. Food is also withheld for twenty-four hours previous to the test.

Young animals seem to respond better than old animals. Probably the ideal for potency testing will be young animals of the same litter. A unit of potency has been defined as one one-hundredth of that amount of extract which produces on an average a 5-mgm rise in blood serum calcium in 20-kilo dogs, over fifteen hours.

No marked and constant variations have so far been noted in the blood constituents of normal dogs other than calcium following single moderate doses of the hormone

Single injections of the parathyroid hormone have not as a rule any ill effect upon dogs unless the dosage is excessive. If the calcium rises above 15 mgm per 100 cc of serum, vomiting may occur, but this in itself is not serious. If massive doses are administered the blood serum calcium may rise to 20 mgm per 100 cc or even higher

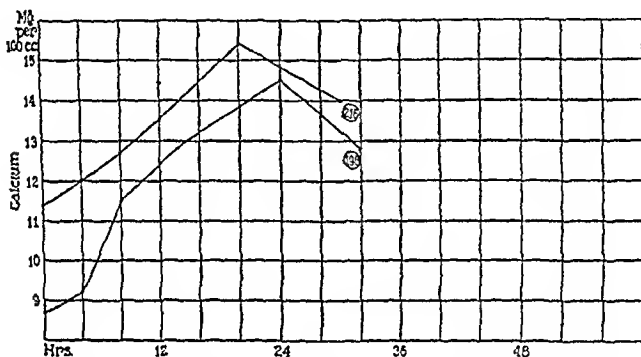


CHART 3 Showing that the response of parathyroidectomized dogs to injections of the hormone is of the same order as the response of normal dogs

Dog 198—19 kilos—thyroparathyroidectomized

Dog 216—18.5 kilos—normal animal

Both animals treated exactly alike, each receiving three injections of the hormone at four hour intervals

and the animal may die on the second or third day. If the condition of profound hypercalcemia is not maintained for an undue length of time, uneventful recovery may occur

#### THE EFFECT OF REPEATED INJECTIONS AT SHORT INTERVALS

Normal dogs injected at four hour intervals with 25 units of parathyroid hormone manifest a typical train of symptoms, run a characteristic blood calcium curve and die within forty-eight to seventy-two hours as a rule. Certain blood constituents other than calcium

also run a characteristic curve. The physical properties of the blood are also altered. Somewhat similar results are obtained when larger or smaller dosage is administered and when the time interval between injections is varied to a considerable degree. The symptoms manifested and the order of their occurrence are somewhat as follows. Some hours after the injections have been begun the animal has attacks of vomiting followed by diarrhea, a certain uneasiness of manner may be manifested at this time but otherwise the animal is quite normal in its behavior. During this period (approximately twenty-four

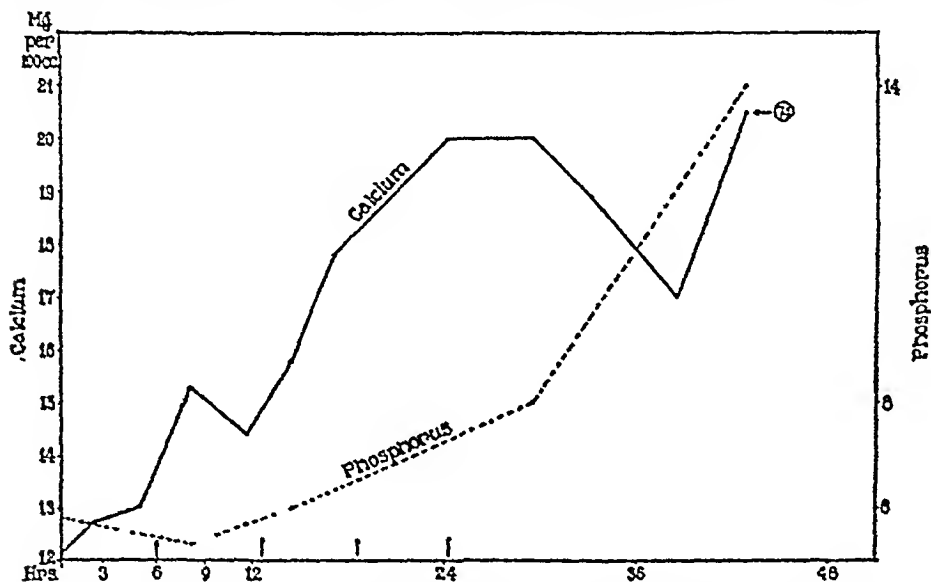


CHART 4 Indicating the blood serum calcium and the whole blood inorganic phosphorus curves, in parathyroid overdosage due to pyramiding in the normal dog

hours) the blood calcium curve is steadily rising at a uniform rate. The peak point of the blood calcium curve is reached at about 20 mgm per 100 cc. It is maintained at this level for some hours and then the blood calcium starts to fall. The animal meanwhile may continue to have occasional attacks of vomiting and diarrhea, and is physically becoming more and more depressed. A certain degree of respiratory distress may also be noted. Coincident with the fall in the blood calcium curve urgent symptoms become manifested. There is vomiting and passing of blood by bowel and the animal passes into a state of collapse. Death follows as a rule within a few hours. In this

period of urgent symptoms the blood phosphorus (inorganic) rises abruptly. The blood urea and non-protein nitrogen also increase several hundred per cent. There is a marked decrease in blood volume and a characteristic thickening of the blood. The coagulation time is decreased. The circulation gradually fails and blood samples are obtained from peripheral veins only with great difficulty. The car-

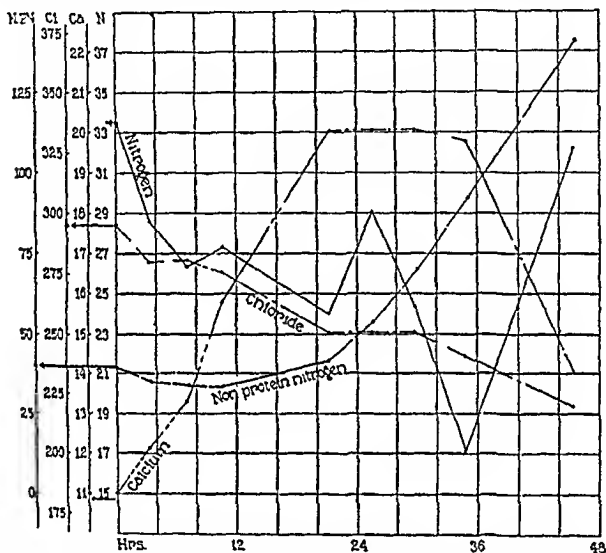


CHART 5 The blood serum calcium, whole blood chloride, nitrogen, and non protein nitrogen, as affected by repeated injections of 25 units of the hormone and frequent bleedings, in the normal dog

bon dioxide content and combining power of the blood serum are as a rule definitely and gradually increased during the first half of such experiments. The pH of the blood serum as determined by the colorimetric method of Cullen may be coincidentally increased very slightly. This would indicate that in this period there is a tendency towards alkalosis which is however well compensated. The increase in  $\text{CO}_2$  content of the blood serum is maintained for several hours, then



this value gradually decreases and in the terminal state is greatly reduced. The pH on the other hand remains stationary until within a few hours of death when it decreases very rapidly. The general effect therefore of parathyroid hormone overdosage upon the acid-base balance is to produce a condition of compensated alkalosis on the first day, this then passes over into a condition of compensated acidosis which in turn is followed by an uncompensated acidosis just prior to death.

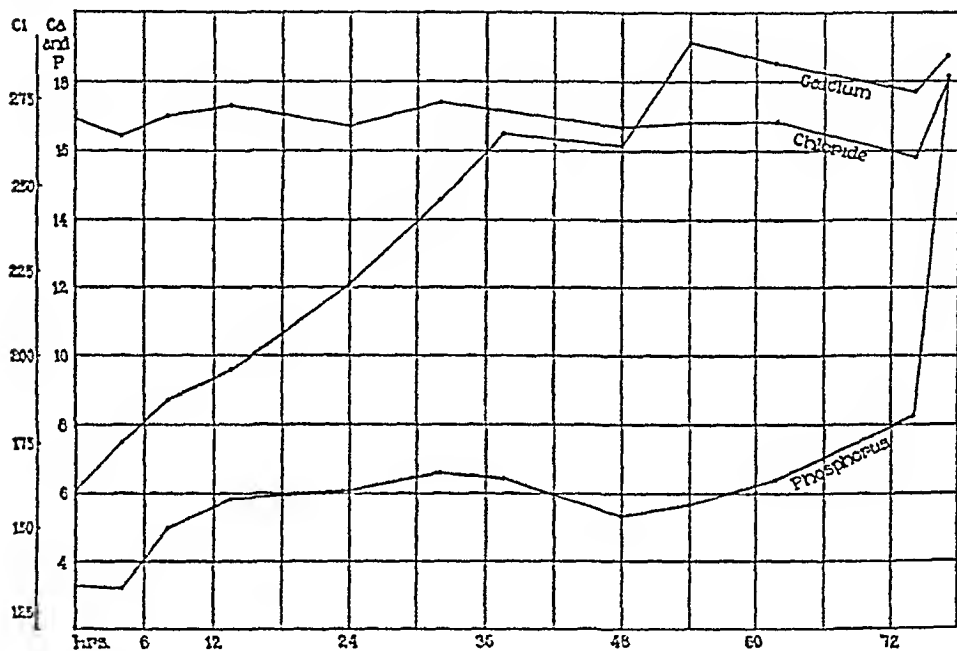


CHART 6 The blood serum calcium and whole blood inorganic phosphorus and chlorides as affected by repeated injections of 25 units of the hormone in a thyroparathyroidectomized dog

The urinary findings in parathyroid hormone overdosage are also of interest. The kidney practically ceases to function very abruptly at about the time that the serum calcium curve has reached its peak point. There is a sudden decrease in the volume of urine produced and, as a rule, both a relative and an absolute decrease in the rate of excretion of phosphorus, ammonia and titratable acid. Coincident with this abrupt decrease in kidney function the curves for whole blood phosphorus, urea, and non-protein nitrogen start to ascend.

These changes and their time relationships are best illustrated by an inspection of the curves in the text

Post-mortem examination of a dog dying from parathyroid hormone overdosage discloses marked congestion of the alimentary canal and the presence of more or less blood in the stomach and intestine

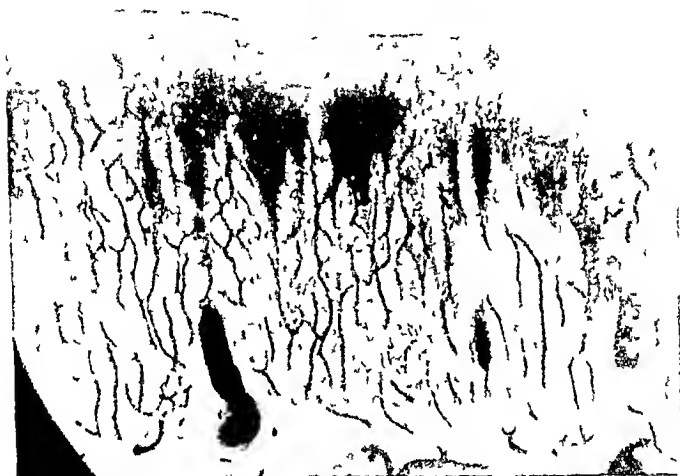


FIG 2 PHOTOMICROGRAPH OF MUCOSA OF STOMACH OF DOG DYING FROM PARATHYROID HORMONE OVERDOSAGE

Note the dilated capillaries and venules, and the hemorrhagic areas. Section prepared by courtesy of Dr R F Shaner

Dr R. Shaner of the department of anatomy of this University has very kindly examined microscopic sections from the stomach of such animals (fig 2) and also of animals dying from injections of calcium chloride and acid sodium phosphate (fig 3). He has described these sections as follows

Sections from the stomach will show a marked change in the blood vessels in the tunica propria, between the gastric glands and gastric pits

As Mall has shown, a fine capillary plexus surrounds the gastric glands

It is fed by arterioles which arise from the submucosal arteries, penetrate the muscularis mucosa and end in the deep part of the capillary plexus. The plexus is drained by small veins which arise superficially between the gastric pits, just beneath the inner surface of the stomach. The veins run back through the tunica propria and muscularis mucosa into the submucosa.

In the stomach of the dog dead from an overdose of parathyroid extract the capillary plexus around the glands, and its veins are moderately dilated,

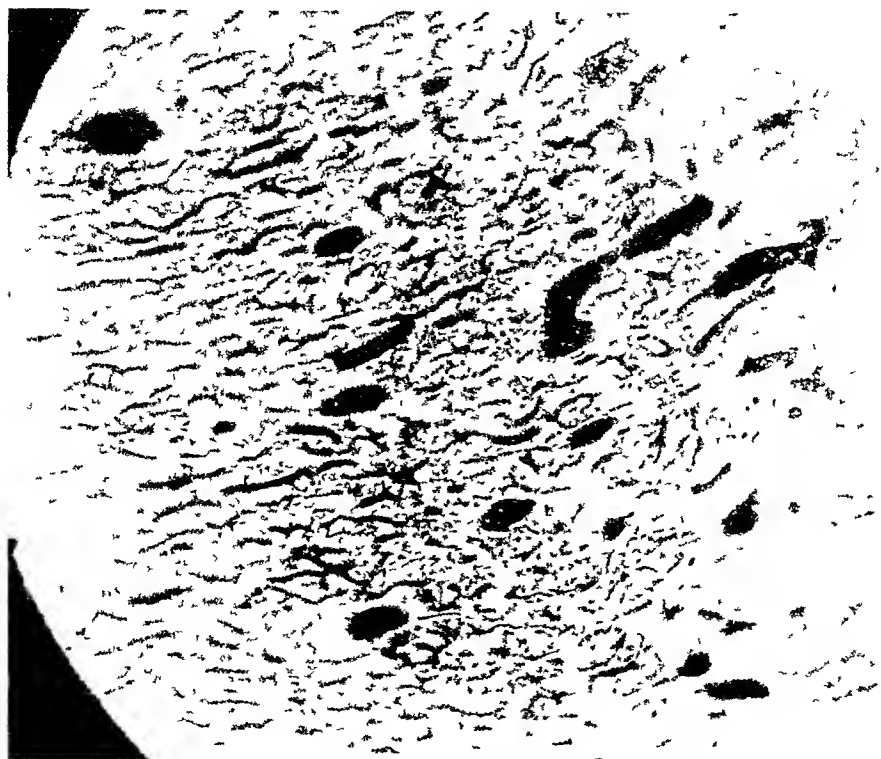


FIG 3 PHOTOMICROGRAPH OF MUCOSA OF STOMACH OF DOG DYING FROM  $\text{CaCl}_2$  AND  $\text{NaH}_2\text{PO}_4$  INJECTIONS

Contrast with figure 2. Section prepared by courtesy of Dr R. F. Shaner

more so superficially where the capillaries pass into the veins. In this superficial zone there is also a general extravasation of blood from the ends of the capillaries and the first parts of the veins into the surrounding tunica propria. There seems to be no actual rupture of endothelial walls, for these can be traced through the cell masses. There is no special dilation of either veins or arteries in the submucosa. Apparently a general diapedesis takes place. The escaping blood first fills the tissue between the gland pits and then seeps out into the stomach cavity.

The stomach of the dog killed by overdose of calcium and phosphorus shows much the same conditions. The capillary-plexus is even more dilated, being affected in the deep as well as in the superficial parts. In the area from which the section was taken no bleeding had occurred, hence no extravasation of blood appears in the sections. There is no doubt, however, that this took place elsewhere, and in the same manner as in the dog killed by parathyroid extract.

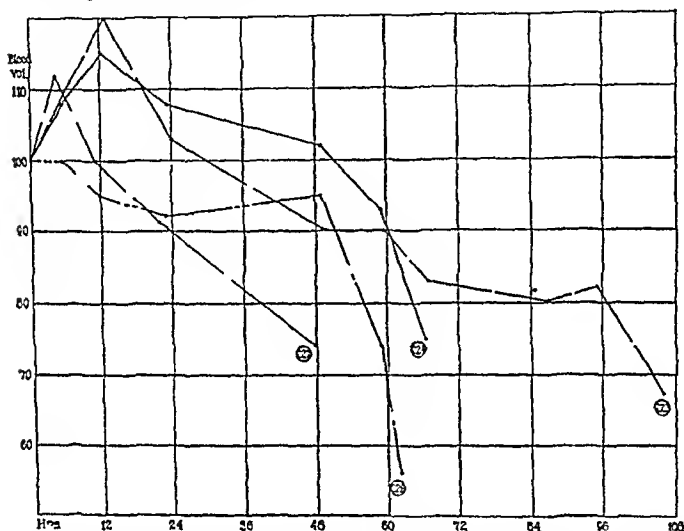


CHART 7 Showing the effect of repeated injections of 25 units of the hormone upon the blood volume as determined by estimation of hemoglobin content

### *Rabbits and rats*

It had been our experience that the normal rabbit and rat are immune to repeated injections of the hormone and indeed showed very little change in blood serum calcium values under such treatment. Macleod and Taylor have obtained similar results. Recently, however, we have shown that hypercalcemia can be induced in most normal rabbits if enormous dosage of the active extract is administered either in single injections or in repeated doses. No effect on inorganic

phosphorus of whole blood was noted in these experiments, neither were any signs of overdosage phenomena produced. These observations taken in conjunction with others which will be referred to in detail later on, force the conclusion that hypercalcemia alone is not deleterious. The overdosage phenomena seen in dogs and cats are in our opinion due to a tripod of conditions, namely, hypercalcemia, hyperphosphatemia and in the terminal stage extreme acidosis. The latter state is in all probability induced by the two former conditions.

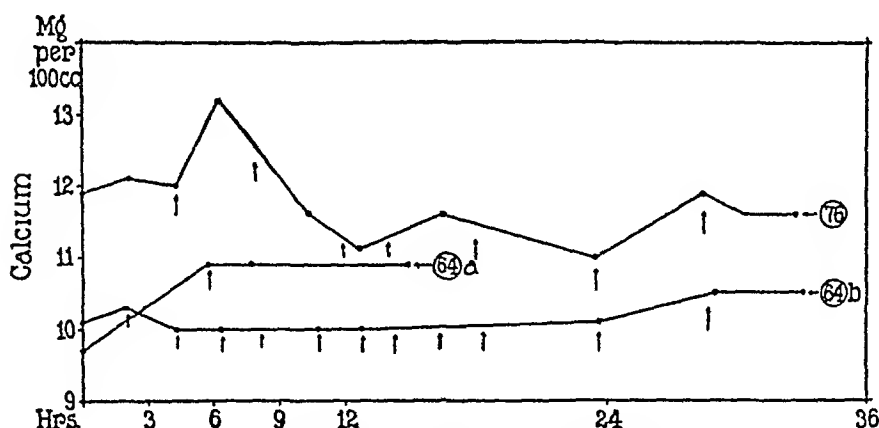


CHART 8 Showing the non-effect of repeated administration *per os* of the parathyroid hormone

#### PARATHYROIDECTOMIZED ANIMALS

##### *Dogs*

The effect of single injections of the active extract into parathyroidectomized dogs is in no way different from the effect on normal animals. There is the characteristic blood calcium curve following the injection. The quantitative response in blood calcium elevation is of the same order as is found in the normal animal. This is of particular interest on account of its bearing on the possible relationship of the thyroid to parathyroid function. As our parathyroidectomized dogs are thyroidectomized as well, the fact, that the effect of the hormone is, as far as one can judge, quantitatively the same in both normal and thyroparathyroidectomized dogs, argues against any influence antagonistic or otherwise of the thyroid upon the parathyroid glands.

Overdosage phenomena and death are produced in thyroparathyroidectomized dogs by repeated injections of the extract just as in the case of normal animals and the same characteristic symptoms and findings are noted

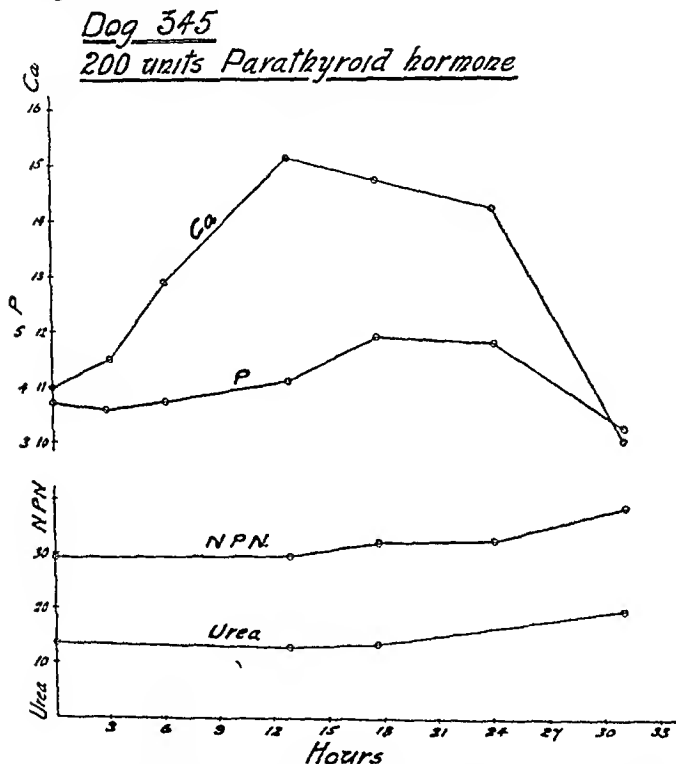


CHART 9 Dog 345, ♂ 25.5 kilos Showing curves for blood serum calcium whole blood inorganic phosphorus, non protein nitrogen and urea following single injection of 200 units of the parathyroid hormone

If the parathyroidectomized animal is in a state of tetany prior to the injection of the active extract there is, coincident with the elevation in the level of blood calcium, relief from tetany and the restoration

of normalcy The production of profound hypercalcemia by overdosage results in the typical symptoms of this condition becoming apparent and death ensuing

The curve of inorganic blood phosphorus in thyroparathyroidectomized animals submitted to overdosage with the parathyroid hormone

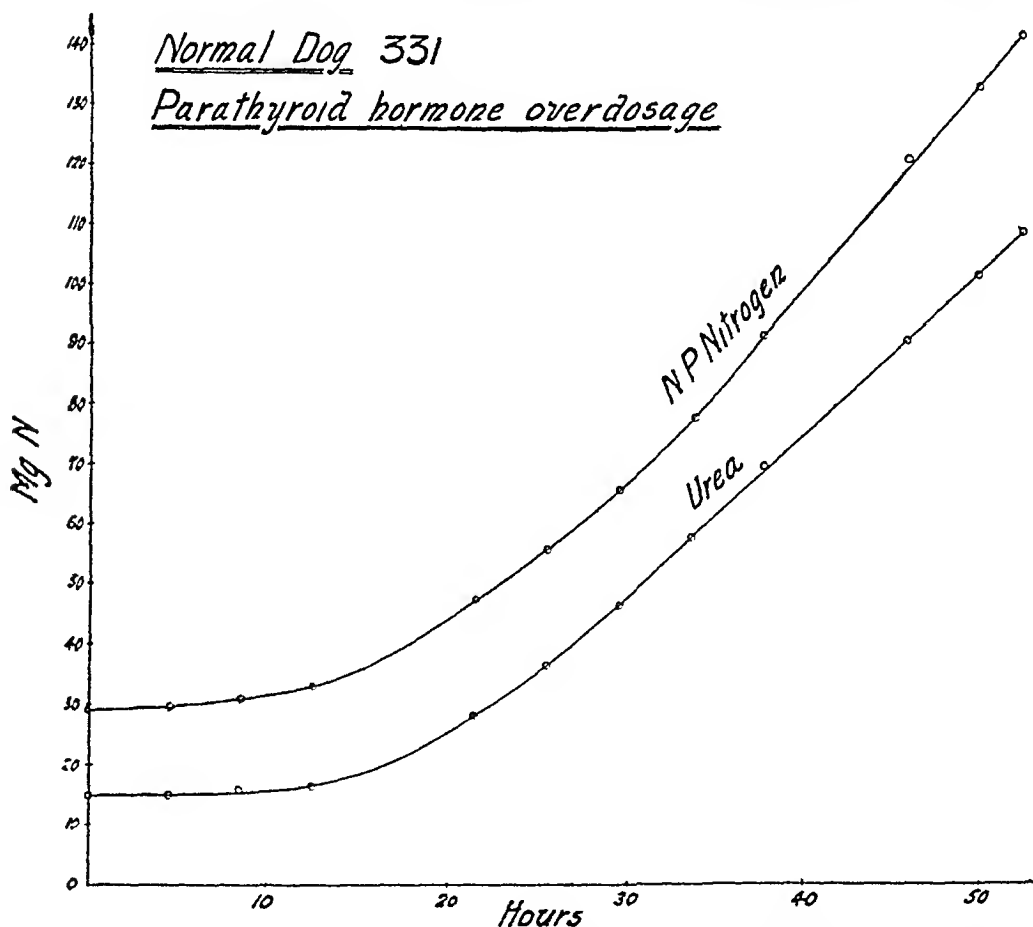


CHART 10 Dog 331, ♂, 18.5 kilos Showing effect of parathyroid hormone overdosage upon the urea and non-protein nitrogen curves The curves compare favorably with those for retention See chart 11.

is of interest It has been our experience that the inorganic phosphorus of the blood of tetany dogs tends to be elevated as Salveson and others have also observed The first effect upon the inorganic phosphorus of the blood induced by injections of the hormone in these animals is as a rule, a reduction to lower values, such as 6 or 7 mgm

reduced to 4 mgm per 100 cc. If overdosage phenomena are produced, however, the inorganic phosphorus rises in the preterminal period to very high levels just as in the case of the normal dogs so treated. Very recently we had the opportunity of treating a case of post-opera-

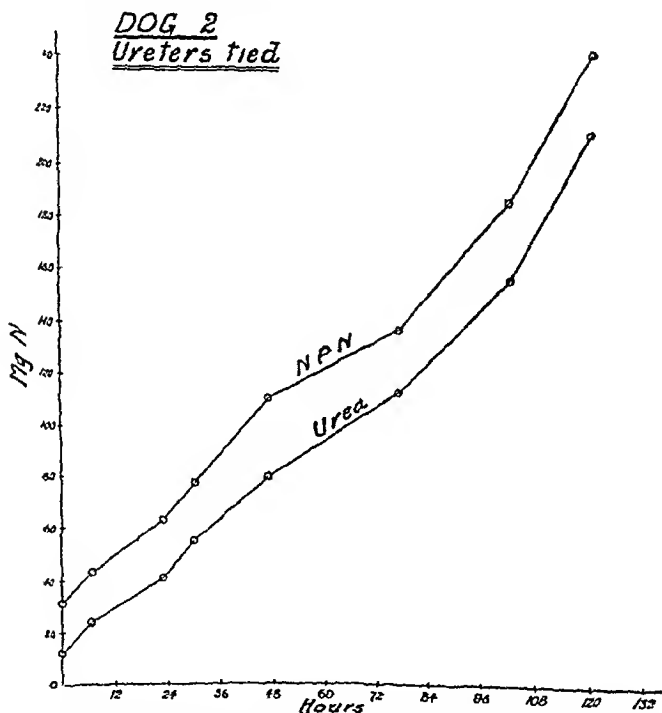


CHART 11 Dog 2, ♀, 16.5 Kilos Both ureters ligated under ether anesthesia. Showing effect of suppression of kidney function upon blood urea and non protein nitrogen

tive hypoparathyroidism in a human subject, with the hormone. The blood serum calcium in this case was 5.5 mgm per 100 cc and the inorganic phosphorus of the whole blood was 7.1 mgm per 100 cc prior to the use of the active extract. In the absence of calcium



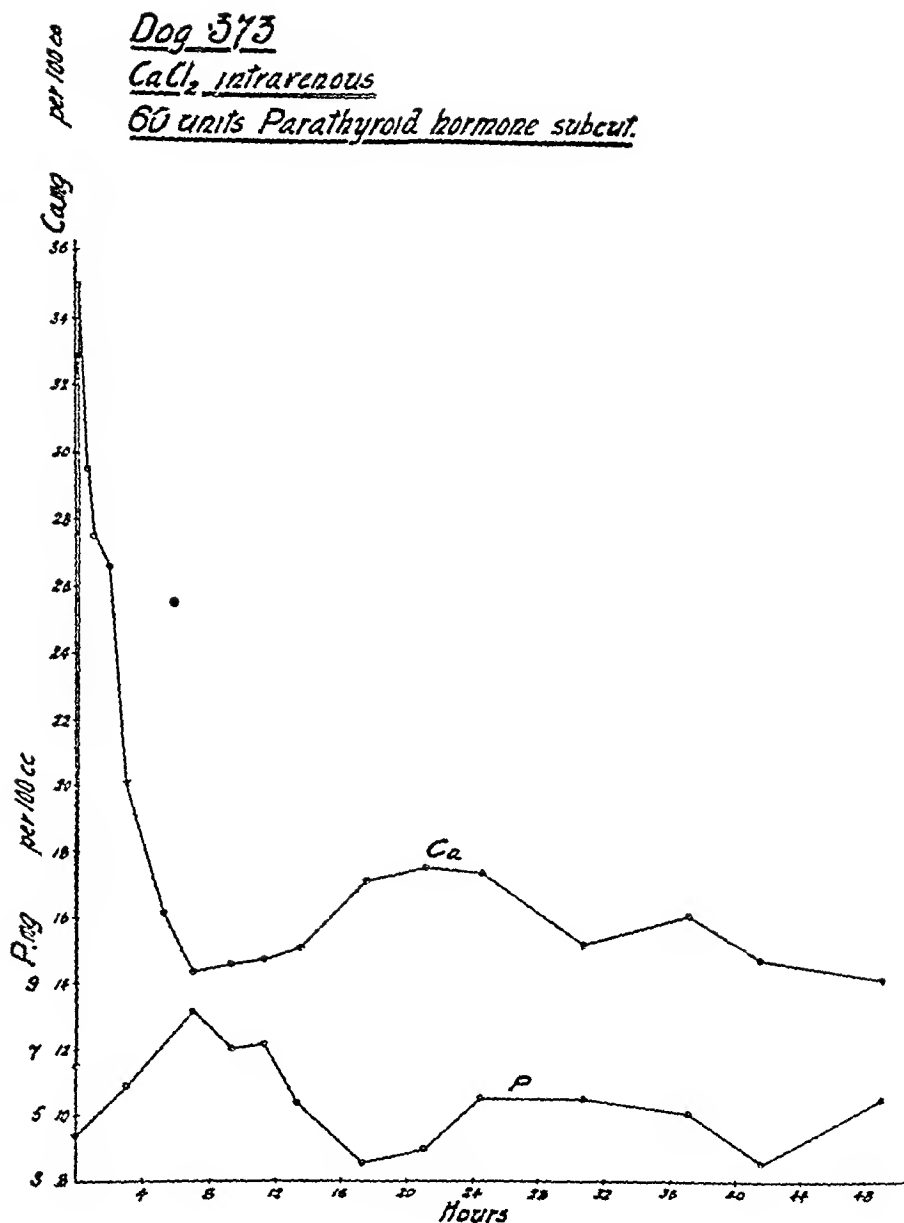


CHART 12 Dog 373, ♂, 14.5 kilos Forty cubic centimeters of 5 per cent  $\text{CaCl}_2$  injected intravenously followed immediately by 60 units of parathyroid hormone subcutaneously. Curves show subsequent effect upon blood serum calcium and whole blood inorganic phosphorus. Note the reinforcing action of the calcium lactate per os upon the calcium curve.

therapy the blood serum calcium was raised to 9.4 mgm and the blood phosphorus reduced to 4 mgm per 100 cc with complete relief of symptoms

### *Cats*

No detailed studies have been made upon parathyroidectomized cats treated with the active extract. Tetany may be prevented or relieved in such animals and the level of blood calcium is raised by the use of the hormone. Overdosage phenomena are similar to those observed in dogs and the terminal rise in blood phosphorus is quite as characteristic.

### *Rabbits*

In view of the fact that normal rabbits are immune to overdosage phenomena and since they show such a sluggish response in the elevation of blood serum calcium following injections of the parathyroid hormone, it is a matter of great interest to study the blood chemistry of these animals as affected by parathyroidectomy and also to observe the effect of the hormone on such parathyroidectomized animals. Such a study has just been completed and the results are very instructive. Removal of the parathyroid glands from normal rabbits has resulted in our experience in the early precipitation of violent tetany, with death following very quickly thereafter. The blood serum calcium starts to fall within a few hours of the operation. During this early period no appreciable changes in blood phosphorus (inorganic) are noted. The onset of fatal tetany is as a rule very rapid. The majority of our untreated animals died within thirty hours. Some hours previous to the onset of tetany and some hours after the blood calcium has started to fall the inorganic phosphorus (as determined by the Briggs method) rises markedly and in the tetany stage reaches very high levels. After tetany is manifested death occurs very rapidly as a rule and injections of parathyroid hormone or even of calcium chloride may be of little avail. The most striking change in the blood chemistry induced by parathyroidectomy in rabbits is the enormous rise in blood phosphorus in the preterminal stage. In this particular these animals differ most from dogs and herein is probably the explanation for the violent and unyielding character of the

tetany manifested in these animals. These observations tend to emphasize the importance of phosphorus in relation to the pathogenesis of tetany, a fact which Greenwald has long maintained to be of great importance.

The treatment of parathyroidectomized rabbits by the injection of the parathyroid hormone can be successfully carried out in the majority of cases providing the injections are started immediately after the operative removal of the glands. A number of parathyroidectom-

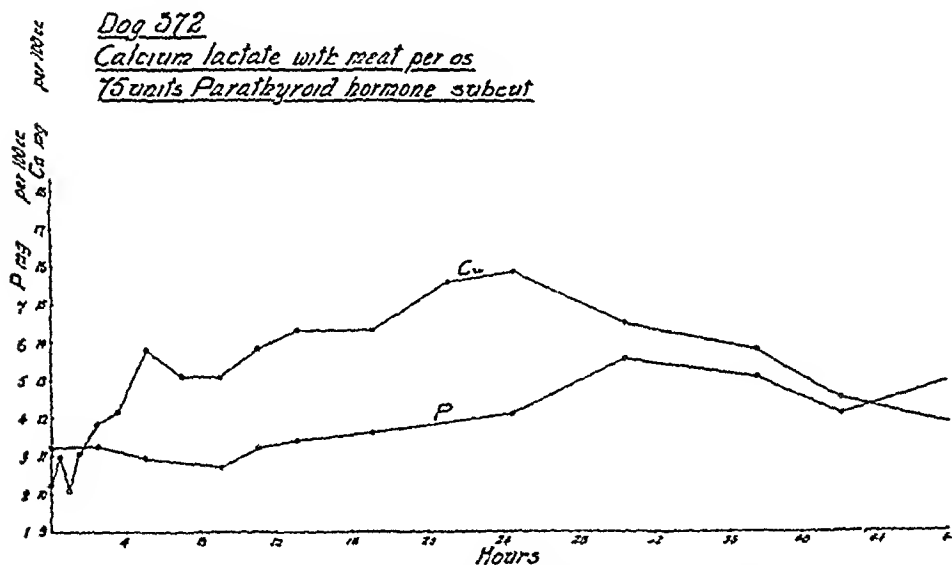


CHART 13 Dog 372, ♂, 16.5 kilos. Seventy-five units of parathyroid hormone injected subcutaneously. Ten grams of calcium lactate fed with lean meat every hour for five hours. Curves show effect upon blood serum calcium and whole blood inorganic phosphorus.

ized rabbits have, however, died during such treatment and at death the blood serum calcium is as a rule only slightly reduced, but the blood phosphorus is found to be very high. Whether such a result is due to too much extract or to an independent break away, so to speak, of the inorganic phosphorus is not yet determined. Certainly by the use of the extract the blood phosphorus may be kept low and the calcium within normal limits in the majority of instances as in the case of parathyroidectomized dogs and cats treated with the hormone.

## IN WHAT FORM DOES CALCIUM EXIST IN THE BLOOD?

As not all the calcium in the blood will dialyze, it has been argued that a certain part of it is organically bound. Cameron and Moorehouse (1925) have very recently published results which indicate the existence in the blood plasma of a specific organic compound of calcium. The findings of Cameron and Moorehouse are of great significance and will be briefly enumerated. Assuming that the cerebrospinal fluid is representative of that part of the plasma which can diffuse through an animal membrane, it is shown that the diffusible calcium of normal dog's plasma averages 53 per cent of the serum calcium. Plasma and serum calcium values of normal dogs are usually equal. Corpuscles are practically calcium free (Kramer and Tisdall (1922), Rona, Petow, and Wittkower (1924)). It is suggested therefore, that 53 per cent of the blood calcium exists in the inorganic form and 47 per cent in organic combination. It is further suggested that in the process of clotting the organic compound of calcium is changed to another organic form which dissociates to a greater extent so that a larger percentage of the serum calcium is diffusible. Removal of the parathyroid glands results in a decrease of the total blood calcium, and of both fractions. There is an apparent gradual increase in the proportion of plasma calcium that can diffuse so that finally, in acute tetany the figures for serum calcium and cerebrospinal fluid calcium tend to become exactly equal. This increase they state, is, however, only apparent since after parathyroidectomy the organic calcium compound with its calcium is more and more completely taken up by the clot so that in acute tetany the serum calcium is less than the plasma calcium by 3 or 4 mgm per 100 cc. This fact, if confirmed, that the plasma calcium and therefore the whole blood calcium, is only slightly reduced in acute tetany while the serum calcium is reduced by approximately 50 per cent of its normal value would seem to throw a new light on the nature of the blood calcium and also on its rôle in parathyroid tetany. Cameron and Moorehouse find that the decrease in whole blood calcium induced by parathyroidectomy is due to a decrease in both the diffusible and non-diffusible forms. The conception of a series of interlocked equilibria between calcium ions and undissociated inorganic calcium compounds

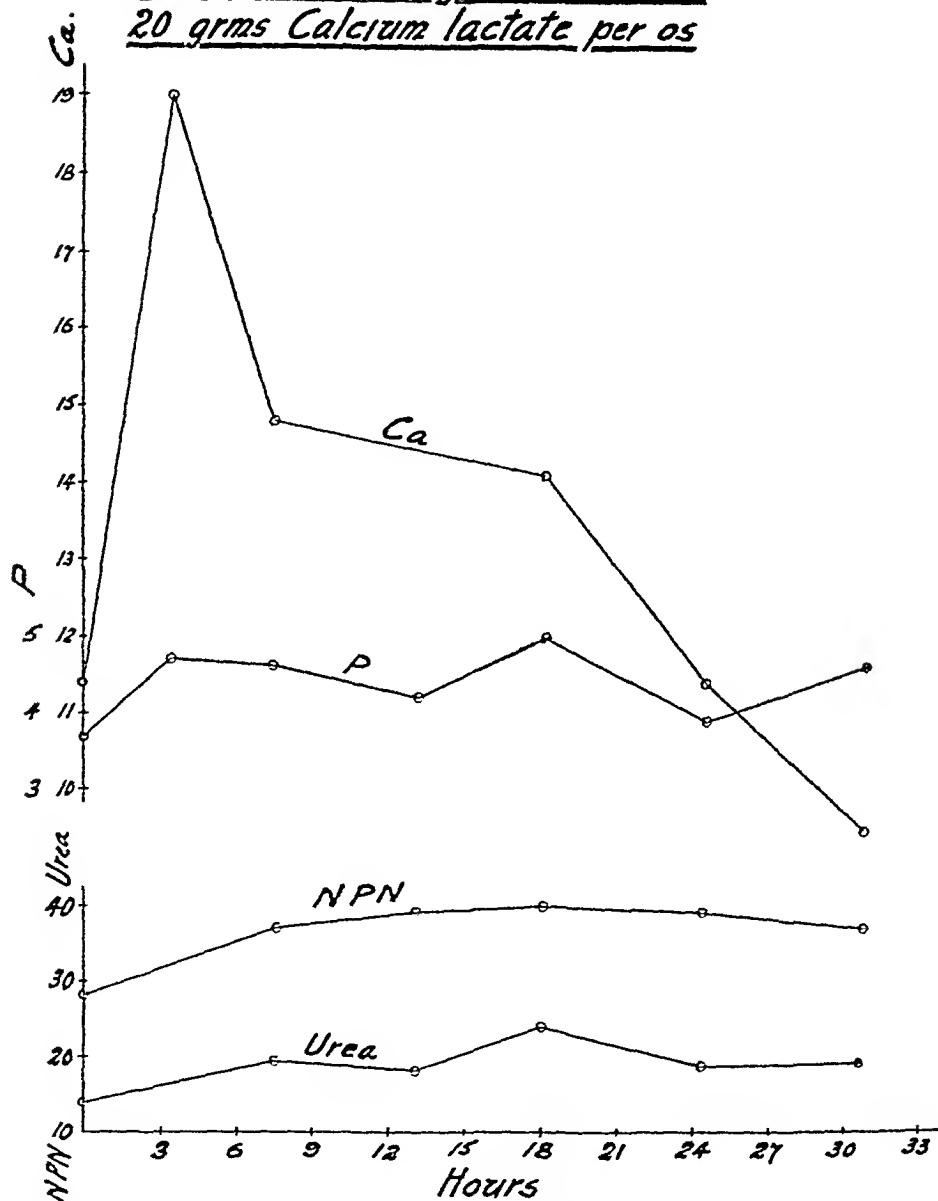
Dog 368.100 units Parathyroid hormone.20 grms Calcium lactate per os

CHART 14 Dog 368, ♀, 17.5 kilos Showing curves for blood serum calcium, and whole blood inorganic phosphorus urea and non-protein nitrogen following single injection of 100 units of the parathyroid hormone Ten grams of calcium lactate were administered by stomach tube at beginning of experiment and again at 37 hours

Dog 371 Wt 15 K  
Calcium lactate per os

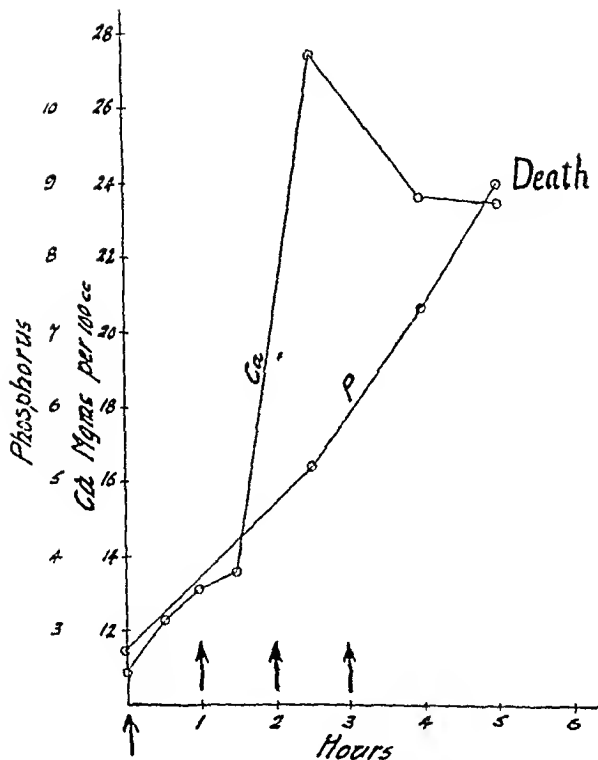


CHART 15 Dog 371, ♀, 15 kilos Ten grams of calcium lactate given by stomach tube at times indicated by arrows on chart. Profound hypercalcemia followed and death ensued. The blood became very viscous and it was difficult to separate the serum therefrom.

and organic calcium ( $\text{CaX}$ ) is presented. Tetany is due to a decrease in the inorganic calcium of the plasma resulting indirectly from a diminution of the organic compound. In testing out the activity of the parathyroid hormone on parathyroidectomized dogs, Cameron and Moorehouse (1925) report as follows. "After injection into the parathyroidectomized animal the serum and plasma values (calcium) rise and tend to become equal, the whole blood calcium increases correspondingly and the cerebrospinal fluid shows a delayed rise"

That the organic calcium compound is entirely convertible into the inorganic form is shown by the fact that ammonium oxalate added to serum results in the quantitative precipitation of the serum calcium. This is only so, however, when sufficient time is allowed to elapse before the recovery of the calcium as the calcium oxalate precipitate is attempted. Such a result is entirely in accord with the theory advanced by Cameron and Moorehouse.

Attention has been focused on the importance of ionized or ionic calcium in the blood (Vines (1921)). No one will dispute the great importance of "ionic" calcium values but until some method is devised which will permit of the accurate determination of the calcium ion-concentration in blood and body fluids, little progress can be made in this field. It is the opinion of the writer that the absolute concentration of calcium ions is the most important factor in calcium metabolism and that this factor is normally regulated either directly or indirectly by the parathyroid glands.

#### THE ESTIMATION OF BLOOD SERUM CALCIUM

Excepting blood phosphorus (inorganic) the determination of the calcium content of the blood serum is the only analytical procedure necessary in studying the effects of parathyroid therapy either in man or animals. There are many chances of error in this determination and to such an extent is this the case that many published reports on blood calcium are valueless because the various possibilities of error have not been eliminated. The method which has been found most satisfactory in our laboratory is a purely empiric one being a slightly modified Tisdall-Kramer procedure (Clark and Collip (1925)). In order that uniform and entirely satisfactory results may be obtained it is necessary to adhere most rigidly to the prescribed tech-

Dogs 340, 344 & 354 Calcium lactate per os  
Dogs 361 & 375 Calcium Chloride per os

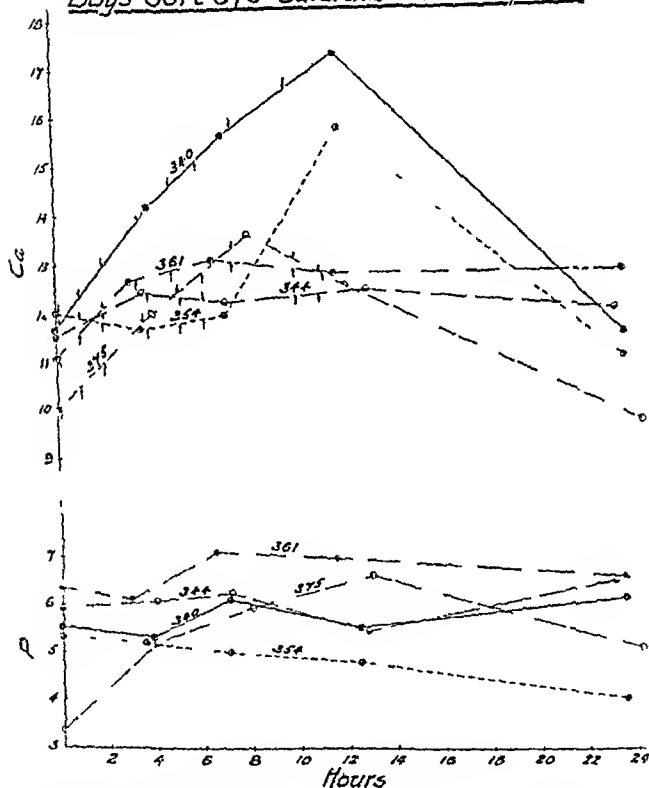


CHART 16 Dog 340, ♂, 18.5 kilos Dog 344, ♂, 12.5 kilos Dog 354, ♂, 18 kilos—thyroparathyroidectomized Dog 361, ♂, 10 kilos Dog 375, ♂, 11 kilos Dogs 340, 344, 354, received 10 grams calcium lactate in 500 cc of water at times indicated on chart Dogs 361 and 375 received 5 grams of calcium chloride in 400 cc of water at times indicated on chart



nique The manner of handling the blood specimen is also of equal importance Care should be observed to separate the serum from the sample, which has been allowed to clot spontaneously, as soon as possible Also, it is most important that the sample should not be chilled (as by being temporarily placed in an ice chest). If the sample cannot be dealt with at once it may be allowed to stand at room temperature for a few hours Chilling of the sample causes a definite decrease in the serum calcium value

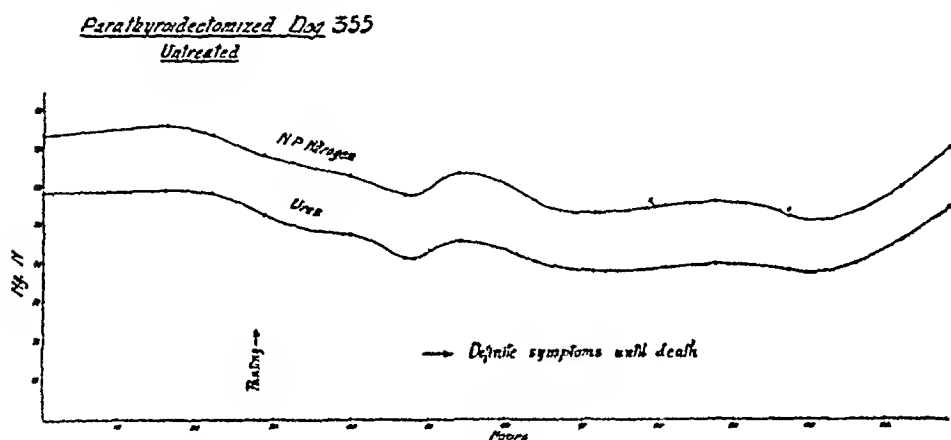


CHART 17 Dog 355, ♂, 22.5 kilos Showing effect of thyroparathyroidectomy upon the blood urea and non-protein nitrogen

### THE RÔLE OF GUANIDINES IN PARATHYROID TETANY

The writer is of the opinion that guanidine intoxication bears no relationship to parathyroid tetany. It is admitted that Paton and his collaborators have made out a strong case for such a relationship and that this theory cannot be summarily dismissed. There is now, however, so much evidence which is not in accord with the guanidine intoxication theory that it is felt that this theory is no longer tenable.

It has been claimed that the injection of guanidine causes a decrease in blood calcium (Watanabe, Sharpe, Gyorgy and Vollmer). Nelken and Salvesson have failed to confirm this as have also Collip and Clark.

Collip and Clark have observed guanidine intoxication in dogs coincident with parathyroid hormone overdosage. No antagonism was demonstrated in these experiments between the parathyroid hormone and guanidine.

Vines (1923) devised a method of estimating the degree of activity of parathyroid preparations which would appear to depend on the degree to which guanidine is destroyed. White and Cameron (1925) have recently applied Vines' method to known potent parathyroid extracts and to certain other substances. They summarize their results as follows:

Vines' method for estimating the activity of parathyroid preparations shows negligible activity when used with Collip's active extract.

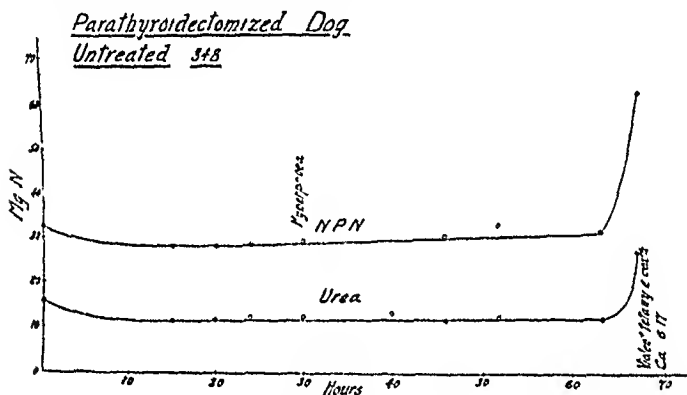


CHART 18 Dog 348, ♂, 24 kilos Showing the effect of thyroparathyroidectomy upon the urea and non protein nitrogen of the blood

Since it appears to depend on the inhibiting influence of complex substances such as arginine or nucleic acid derivatives on the precipitation of guanidine picrate, such results as have been obtained by Vines for animal tissues (using this method) probably bear no relation to the function of those tissues.

In a recent communication Collip and Clark (1925) report on the nature of the urea and non-protein nitrogen curves for the blood of untreated parathyroidectomized dogs. It was found that the urea and non-protein nitrogen curves run practically parallel throughout an experiment. Just before death occurs, there may be slight deviation of the curves. The curves fail to show any evidence of the accu-

Spontaneous tetany occurred thereafter at irregular intervals and was rapidly controlled by the oral administration of calcium lactate and the giving of enemas

Salveson (1923) observed that dogs in a state of latent tetany, but showing no symptoms, months after complete parathyroidectomy still have a low serum calcium and a slightly elevated inorganic phosphorus

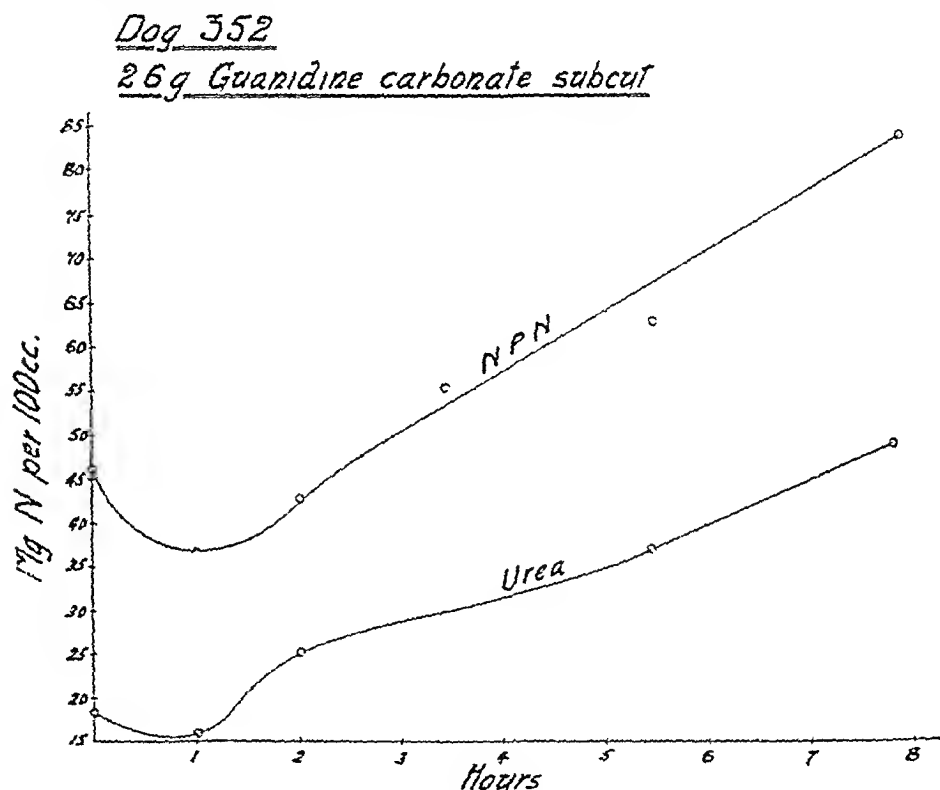


CHART 20 Dog 352, ♂, 17 kilos 26 grams of guanidine carbonate injected subcutaneously

It has been observed in our own laboratory that certain parathyroidectomized dogs which have been kept in a normal condition for six weeks or more by the daily injection of parathyroid hormone will suffer no immediate ill effects from withdrawal of the treatment. Such animals develop tetany during periods of heat. The blood serum calcium remains at a low level for an indefinite period. Other animals cannot be kept free from tetany under similar dietary conditions (exclusive lean meat diet) unless the treatment is continued.

A rational explanation of these observations is that accessory parathyroid tissue is present in certain instances. Salveson does not accept this view and states that if true parathyroid function were manifested the blood serum calcium should be restored to higher levels. In the light of our own observations that the action of the parathyroid hormone is quantitative, this criticism is not valid. It is the writer's opinion that in true latent tetany parathyroid function is being maintained to a degree and that in the absence of any parathyroid function, tetany on a meat diet is unavoidable. In this latter condition life can only be maintained indefinitely by injections of the hormone or by other therapy designed to maintain the calcium and inorganic phosphorus of the blood within definite bounds (see legend figure 4—dog 48)

#### THE EFFECT OF DIET AND THE STATE OF NUTRITION UPON THE RESPONSE TO INJECTIONS OF THE PARATHYROID HORMONE

Since dogs and cats are very sensitive to injections of the hormone, and rabbits, guinea pigs and rats are resistant to such injections, it is logical to suppose that the dietary habits of a species might influence the response to the parathyroid hormone. In our own limited experience changing the diet of dogs used in potency testing from lean meat to bread has had very little influence upon the response of these animals to injections of the extract.

Macleod and Taylor have observed that a very fat dog, which responded very sluggishly to the hormone became very sensitive to it after its body fat had been reduced. No doubt further investigation will show that there are many factors which can affect the response to injections of the active extract. The nutritional condition is at least one factor which has this effect.

#### PARATHYROID HORMONE, ULTRA-VIOLET LIGHT AND THE ANTI-RACHITIC VITAMINE

It is apparent that there is some fundamental relationship between the physiological effects of the parathyroid hormone, of the action of ultra-violet radiations and of the anti-rachitic vitamine. That the action of the former is upon calcium metabolism is proven. It is a possibility that the latter two agents act upon phosphorus metabolism.

Spontaneous tetany occurred thereafter at irregular intervals and was rapidly controlled by the oral administration of calcium lactate and the giving of enemas

Salveson (1923) observed that dogs in a state of latent tetany, but showing no symptoms, months after complete parathyroidectomy still have a low serum calcium and a slightly elevated inorganic phosphorus

Dog 352

26 g Guanidine carbonate subcut

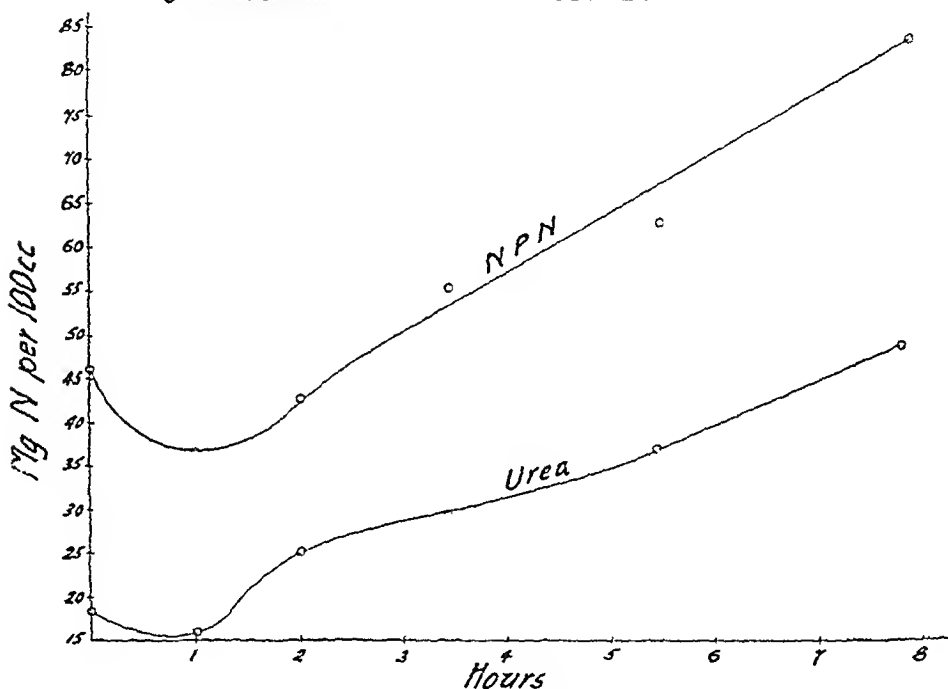


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It remains however for future research to give an adequate answer to this question

#### GENERAL DISCUSSION

The recent preparation and standardization of active parathyroid extracts and the study of their physiological action has confirmed the theory of MacCallum and the more recent work of Salveson on the relationship of parathyroid function to calcium metabolism. Although MacCallum and Voegtlin discovered the favorable effect of calcium in tetany in 1909, it has only been of late that completely parathyroidectomized animals have been kept in a normal state for long periods of time by vigorous calcium therapy. The parathyroidless animal loses the power to maintain calcium in the blood. Salveson has shown that this defect may be overcome by artificially forcing up the level of the blood calcium. He has also demonstrated that this process must be more or less continuous since injected calcium leaves the circulation very rapidly and may be quantitatively recovered in the excreta. Greenwald<sup>4</sup> (1925) finds that the parathyroid hormone administered to normal animals causes an increase in the excretion of calcium. This may be directly due to the increased calcium content of the blood. Calcium injected into the blood stream of the normal animal leaves the circulation very rapidly as Salveson has shown and we have confirmed. It is quite to be expected therefore when the blood calcium is increased in a normal animal by the use of the hormone that there will be an increased excretion of this element. The hormone must be looked upon essentially as a mobilizer of calcium. The native production and liberation of the hormone in the normal animal must be just such as will maintain a dead level of calcium in the blood stream. Since it requires a minimum of 15 units per day to keep a parathyroidectomized animal free from symptoms it is probable that the daily production in the normal human subject would be at least three times this amount.

Recent blood chemistry studies in parathyroidectomized rabbits indicate that the rôle of phosphorus in tetany has not been sufficiently stressed (Collip (1925)). The inorganic phosphorus in this animal

<sup>4</sup> Personal communication

increases enormously after removal of the parathyroid glands and tetany of the most marked type quickly develops (under thirty hours as a rule), and death follows shortly thereafter. Injections of parathyroid hormone or even of calcium chloride may be of no avail once marked tetany has become manifested. The blood calcium is found to be lowered just as in the case of the parathyroidectomized dog or cat. These animals may still die after the calcium has been raised several milligrams per cent by injections of the parathyroid hormone.

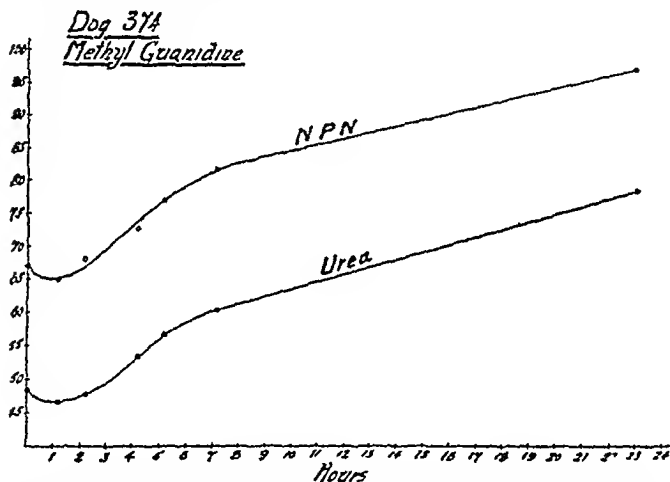


CHART 21 Dog 374, ♂, 20 kilos. Showing effect of the subcutaneous injection of 2 grams of methyl guanidine (sulphate) upon the blood urea and non protein nitrogen. Death occurred on the third day following the injection.

If treatment with the hormone is instituted immediately after the operative removal of the glands most animals may be maintained in a normal state for some days. Death may occur suddenly, however, in certain of these animals and blood analysis may then show a practically normal calcium but a markedly increased inorganic phosphorus content (20 mgm per cent). This increase in phosphorus is not due to the extract unless the parathyroidectomized rabbit has some peculiar sensitivity to it which is not seen in the dog, because normal rabbits



are practically immune to any ill effects of parathyroid hormone overdosage. Enormous dosage may cause marked increases in blood calcium values but phosphorus does not change materially. Since the urgent symptoms of overdosage with the hormone seen in dogs and cats are coincident with a falling calcium curve and a rising phosphorus curve, it is probable that these urgent symptoms are due more to the blood phosphorus change than to the high blood calcium. Granted that this is true, then a rise in blood phosphorus would be the natural

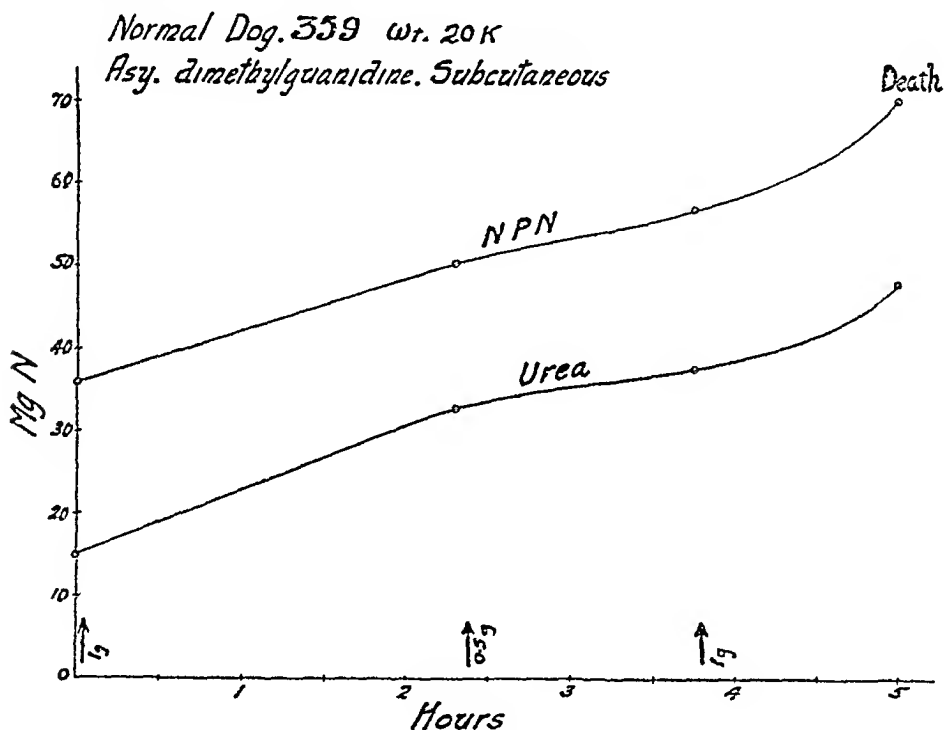


CHART 22 Dog 359, ♂, 20 kilos 25 grams of asymmetric dimethyl guanidine (sulphate) administered as indicated on the chart. Mild tetany was manifested three and one-half hours after experiment was started.

danger signal of overdosage rather than the blood calcium value. It would also furnish a rational explanation of the difference in the toxic effect of the hormone in different animals.

#### *Overdosage phenomena in dogs simulated by means of inorganic salts*

In an endeavor to discover the cause of the characteristic phenomena manifested in dogs submitted to overdosage with the parathyroid

hormone, certain inorganic salts have been injected intravenously into normal animals. As a result of this investigation it may be stated that, by injections of calcium chloride and acid sodium phosphate solutions, a condition very similar to that seen in the preterminal state of parathyroid hormone overdosage may be produced. Neither calcium chloride nor sodium acid phosphate solutions alone administered by intravenous injections have produced this effect. Relatively enormous amounts of calcium chloride can be administered

Dog 376

500 mg Urea per kilo Subcutaneous

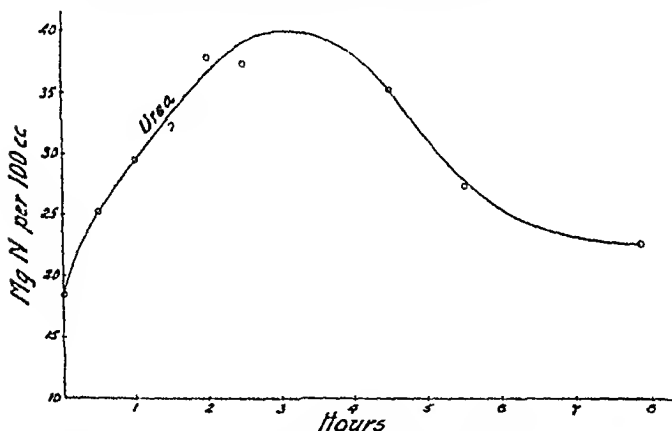


CHART 23 Dog 376, ♀, 8 kilos Four grams of urea in 20 cc of water injected subcutaneously. Curve shows subsequent effect upon blood urea.

by intravenous injection if the injection rate is sufficiently slow. Salveson has shown that injected calcium leaves the circulation very rapidly. This has been confirmed but it has also been demonstrated that a blood serum calcium content of approximately 20 mgm per 100 cc is borne well even when it is maintained (by artificial means) over many hours. When the blood serum calcium is maintained at this level by repeated injections of calcium chloride the blood phosphorus (inorganic) is increased but not to the extent seen in parathy-

roid hormone overdosage. Our results in this particular are in accord with those of Salveson.

Binger has shown that the injection of either neutral or basic phosphate solutions lower blood calcium and induce tetany. Acid phosphate solutions, however, did not produce tetany but did cause a decrease in blood calcium values. Tisdall (1922) obtained similar results. We have found that phosphate mixtures adjusted to the pH of blood are well tolerated if calcium chloride is also administered in adequate amounts. Under these conditions the blood calcium and blood phosphorus (inorganic) tend to be kept at much lower levels than when acid phosphate and calcium are administered. No doubt in the former case both the injected calcium and phosphate are very rapidly disposed of as  $\text{Ca}_3\text{PO}_4$ .

Not only are the terminal symptoms of parathyroid hormone overdosage simulated by intravenous injections of calcium chloride and acid sodium phosphate but also the post-mortem findings are practically identical. There is marked congestion of the alimentary canal with diffuse hemorrhage through the mucosa into the lumen. Microscopic sections of the wall of the stomach are practically indistinguishable from similar sections obtained from the tissue of an animal killed by hormone overdosage. (Compare figures 2 and 3)

One may conclude therefore that it is a combination of hypercalcemia and hyperphosphatemia associated with a condition of acidosis which kills. The cause of the preterminal hyperphosphatemia in parathyroid overdosage in dogs and cats is not yet absolutely revealed. Prolonged hypercalcemia in itself, may be the sole cause of the delayed hyperphosphatemia. One cannot state with absolute assurance, however, that this is the only causative factor. It would appear that the unequal response of different species in phosphate mobilization may be an explanation of the variable tolerance to the active extract as seen for example in the dog and the rabbit.

*Oral administration of calcium lactate in conjunction with subcutaneous injections of the parathyroid hormone*

Calcium therapy as an adjuvant in connection with treatment by means of the parathyroid hormone has been deliberately avoided in all the earlier work with the active extract. This was done in order

that the merits of the hormone might be proven. Now that this has been done, it would seem obvious that a rational therapy should consist of a combination of calcium given by the oral route and of the active extract given by subcutaneous injection. The effectiveness of the hormone is greatly enhanced when calcium lactate is given per os. Animal experimentation has shown that there may be an element of danger in the oral administration of calcium lactate. Thus we have observed most profound hypercalcemia resulting in death in a period of five hours as a result of the oral administration to a fasting dog of 10 grams of calcium lactate at intervals of one hour. In this experiment the drug was administered by the use of the stomach tube and considerable water was used as a vehicle. The blood serum calcium and the whole blood inorganic phosphorus curves obtained in this experiment are shown in chart 15. With the development of the condition of hypercalcemia the blood became very viscous and the final sample was so viscous that only 1 cc. of serum was obtained from 20 cc. by the use of a high power centrifuge. At death the stomach and intestine were hyperemic but hemorrhage had not occurred into the lumen.

This remarkable result is attributed to the filling of the alimentary tract with a solution of a soluble calcium salt. Absorption would thereby be facilitated in the upper and excretion inhibited in the lower part of the intestine. Attempts to duplicate this experiment have so far failed. The usual effect of repeated oral administration of calcium is shown in chart 16.

This latter result stands in marked contrast to those obtained by the feeding of the lactate in solid form along with meat or by the intravenous injection of a solution of calcium chloride and the simultaneous injection of a moderate dose of the hormone. (See charts 12 and 13.)

Dr. Aub<sup>5</sup> has observed that certain human subjects showing only slight response in the blood serum calcium on 50 units of extract per diem developed serum calcium values as high as 19 mgm. per 100 cc. when calcium lactate was added to the diet.

It is therefore evident that, by the intelligent use of a combination

<sup>5</sup> Personal communication. Quoted by courtesy of Dr. Aub.

Post-operative hypoparathyroidism.  
(Adult human. Age 34 ♂)

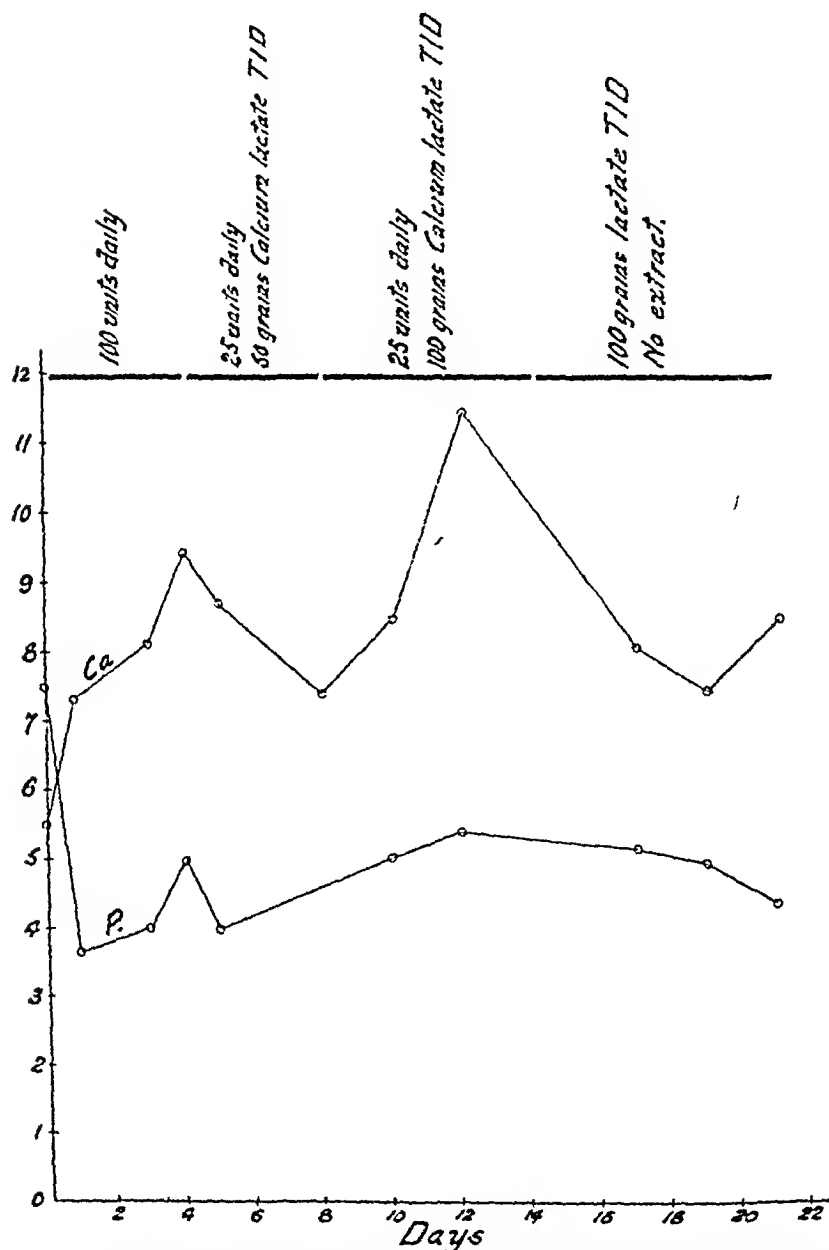


CHART 24 Post-operative hypoparathyroidism treated with parathyroid hormone and calcium lactate as indicated on the chart. An excellent clinical result was obtained.

of calcium therapy and injections of the parathyroid hormone, calcium metabolism can be influenced just as surely as sugar metabolism is influenced by insulin

*Dog 382 ♂ wt 18.5 Kilos*

*Parathyroid hormone Overdosage*

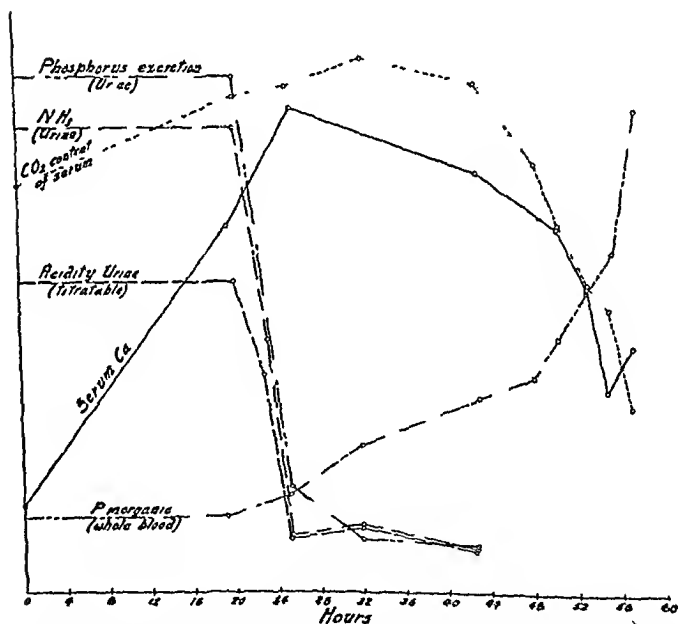


CHART 25 Showing the effect of parathyroid hormone overdosage upon the CO<sub>2</sub> content of the serum, the serum calcium and whole blood inorganic phosphorus. The rate of excretion of phosphorus and ammonia in the urine and the titratable acidity are also illustrated. Note that there is almost complete cessation of kidney function in the latter part of the experiment. It is in this period that phosphorus, urea and non-protein nitrogen increase in the blood. The pH of the serum may increase very slightly during the first half of such an experiment. In the last few hours just prior to death the pH is markedly decreased.

*The parathyroid hormone as a useful therapeutic agent*

Sufficient clinical investigation with the active parathyroid extract has now been carried out to indicate that it will have a very definite place in the therapeutic armamentarium. It will be of greatest value no doubt in those cases in which a condition of hypoparathyroidism exists. Post-operative tetany and infantile tetany are generally recognized as belonging in this class. Recent researches of Scott, Ashford, White and Fleming and others would seem to disclose a condition of hypoparathyroid function in tropical sprue. Further work may show that certain other conditions may be complicated by a mild hypoparathyroidism. The use of the hormone would appear to be definitely indicated as yet only in those cases in which hypoparathyroidism exists.

As calcium enters into the mechanism of so many physiological processes, it is possible that clinical research will later indicate that it is desirable under certain definite circumstances to produce a state of mild hypercalcemia.

A number of cases of hypoparathyroidism in which the hormone has been successfully used have been reported.

Collip and Leitch reported a case of tetany in a young child successfully treated with the parathyroid hormone.

Davidson has reported the use of the active extract in a case of chronic tetany associated with myxedema and nephrosis.

Crile has reported the successful use of the active extract in a number of cases of post-operative tetany.

Snell has reported a case of chronic post-operative tetany treated with calcium and the parathyroid hormone. The dosage of each was so adjusted in this case that neither agent alone would maintain the level of blood calcium within normal limits, while combined, the desired result was obtained.

Lisser has treated a case of post-operative tetany with the hormone with excellent results.

Collip and Blais have recently treated a case of post-operative hypoparathyroidism of unusual type. A most satisfactory result was obtained. The blood chemistry of this case is shown in chart 24.

Petty, Stoner and Schaffer have used the hormone in a number of

very carefully controlled cases and report on the specific effect of the extract in the mobilization of blood serum calcium

Numerous unpublished clinical reports have been furnished to me through the kindness of many clinicians in various parts of the continent, who have been using the extract in an experimental manner. The results in general corroborate entirely the experimental results obtained in the laboratory.

Experimental clinical work is now being carried on in conditions other than hypocalcemia. As results are obtained they will be published.

## REFERENCES

- ABEL, J. J., AND GEILING, F. M. K. *J Pharm and Exp Ther*, 1925, xxv, 423  
 BARKER, L. *Endocrinology and Metabolism*, New York, 1922, vol 1, 577  
 BARKER, L. AND SPRUNT. *Endocrinology*, 1925  
 BERKELEY, W. N., AND BEEBE, S. P. *J Med Research*, Boston, 1909, xx, 149  
 BERMAN, L. *Proc Soc Exper Biol and Med*, 1924, xxi, 465  
 BIEDL, A. *The Internal Secretory Organs*, New York, 1913, 56  
 BINGER, C. *J Pharm and Exper Ther*, 1917-18, x, 105  
 BLUMENSTOCK, J., AND ICKSTADT, A. *J Biol Chem*, 1924, lxi, 91  
 BORCHERS, E. *Zentralbl f chir*, 1919, xlv, 907  
 BRIGGS, A. P. *J Biol Chem*, 1922, lvi, 13  
 CAMERON, A. T., AND CARMICHAEL, J. (a) *Trans Roy Soc Can*, 1922, xvi, Sect V, 57 (b) *Trans Roy Soc Can*, 1925, xix, Sect V 53  
 CAMERON, A. T., AND MOOREHOUSE, V. H. K. (a) *J Biol Chem*, 1925, lxxii, 687 (b) *Trans Roy Soc Can*, 1925, xix, Sect V 39  
 CAMPBELL, J. A. *J Physiol*, 1925, lx, 347  
 CLARK, E. P., AND COLLIP, J. B. (a) *J Biol Chem*, 1925, lxxii, 461 (b) *J Biol Chem* (in press)  
 COLLIP, J. B. (a) *Amer J Physiol*, 1920, li, 483 (b) *Can Med Assoc Journ*, 1920 (c) *J Biol Chem*, 1925, lxxii, 395 (d) *Amer J Physiol*, 1925, lxxii, 182 (e) *Proc Nat. Acad Sc*, 1925, ii, 494 (f) *International Clinics*, 1925, iii, 77 (g) *Annals Clin Med*, 1925, iv, 219 (h) *Proc Fed Amer Soc Exper Biol*, Cleveland Meeting, 1925  
 COLLIP, J. B., AND BACRUS, P. L. *Amer J Physiol*, 1920, li, 568  
 COLLIP, J. B., AND CLARK, E. P. (a) *Trans Roy Soc Can*, 1925, xix, Sect V, 25 (b) *J Biol Chem*, 1925, lxxv, 485 (c) *J Biol Chem*, 1925, lxxvi (d) *Proc Amer Soc Biol Chem*, Cleveland Meeting, 1925  
 COLLIP, J. B., CLARK, E. P., AND SCOTT, J. W. *J Biol Chem*, 1925, lxxii, 439  
 COLLIP, J. B., AND LEITCH, D. *Can Med Assoc Journ* 1925, xv, 59  
 COWDRY, E. V. *Endocrinology and Metabolism*, New York and London, 1922, vol 1, 501  
 CRILE, G. W. *Endocrinology*, 1925, ix, 301  
 DAVIDSON, J. R. *Can Med Soc*, 1925, xv, 803



- DRAGSTEDT, L R., AND PEACOCK, S C *Amer J Physiol*, 1923, *lxiv*, 424
- EISELSBERG, A *Festsch f Billroth Stuttgart*, 1892 Quoted from *Biedl Internal Secretory Organs*
- ELIAS AND SPIEGEL, *Wien Arch f innere Med*, 1921, *ii*, 447
- ELIAS, AND WEISS *Wien Arch f innere Med*, 1922, *iv*, 59
- FINDLAY AND SHARPE *Quart J Med*, 1920, *xliii*, 433
- FISHER H F, AND LARSON, E *Amer J Physiol*, 1925, *lxxv*, 93
- FRANK, STERN AND NOTTHMANN *Zeitsch f ges exp Med*, 1921, *xxiv*, 341
- GLEYS, E (a) *Compt rend soc de biol*, Paris, 1891, *iii*, 551, 841, and 843 (b) *Gaz Med de Paris*, 1892, *i*, 464
- GRANT, S B, AND GOLDMAN, A *Amer J Physiol*, 1920, *li*, 209
- GREENWALD, I (a) *Amer J Physiol*, 1911, *xxviii*, 103 (b) *J Biol Chem*, 1913, *xiv*, 363 (c) *J Biol Chem*, 1922, *lv*, 285 (d) *J Biol Chem*, 1924, *lvi*, 33
- GYORGY AND VOLLMER *Arch f exp Path u Pharm*, 1922, *xcv*, 200
- HALSTED, W S *J Exper Med*, 1909, *xi*, 175
- HANSON, A M *Mil Surg*, 1924, *liv*, 79, 218 and 554
- HARROD, G A, JR *Bull Johns Hopkins Hosp*, 1919, *xxx*, 62
- HJORT, A M, ROBISON, S C, AND ZENDICK, F H *J Biol Chem*, 1925, *lxxv*, 117
- JOSEPH, D R, AND MELTZER, S J *J Pharm and Exp Ther*, 1911, *ii*, 271
- KOCH W F (a) *J Biol Chem*, 1912-13, *xii*, 313 (b) *Ibid*, 1913, *xv*, 43
- KOHN, A *Arch f mikr Anat Bonn*, 1895, *xliv*, 366
- KRAMER, B, AND TISDALL, F F *J Biol Chem*, 1922, *liii*, 241
- KRAMER, B, TISDALL, F F, AND HOWLAND, J *Amer J Dis Child*, 1921, *xvii*, 431
- KUSSMAUL, A *Berlin Klin Wehnschr*, 1872, *ix*, 441
- LISSER, H, AND SHEPARDSON, H C *Endocrinology*, 1925, *ix*, 383
- LOEB, J *Amer J Physiol*, 1901, *v*, 352
- LUCKHARDT, A B, AND BLUMENSTOCK, J *Science*, 1922, *lvi*, 257
- LUCKHARDT, A B, AND COMPERE, E T *Proc Soc Exp Biol and Med*, 1924, *xvi*, 523
- LUCKHARDT, A B, AND GOLDBERG, B *J Amer Med Assoc*, 1923, *lxxx*, 79
- LUCKHARDT, A B, AND ROSENBLUM, P J (a) *Proc Soc Exp Biol and Med*, 1921-22, *xix*, 129 (b) *Science*, 1922, *lvi*, 48 and 257
- MACCALLUM, W G (a) *J Amer Med Assoc*, 1912, *lix* 319 (b) *Medicine*, 1924, *iii*, 137
- MACCALLUM, W G, LAMBERT, R A, AND VOGEL, K M *J Exper Med*, 1914, *xx*, 149
- MACCALLUM, W G, AND VOETGLIN, C *J Exper Med*, 1909, *vi*, 118
- MACLEOD, J J R, AND TAYLOR, N B *Trans Roy Soc Can*, 1925, *xix*, Sect V, 27
- MCCANN, W S *J Biol Chem*, 1918, *xxxv*, 553
- MORRIS, — *Brit J Exper Path*, 1922, *iii*, 209
- MOUSSU, G *Compt rend Soc de biol Paris*, 1897, 10 s, *iv*, 44 1898, 10 s, *v*, 867
- NATTRASS AND SHARPE *Brit Med J*, 1921, *ii*, 28
- NELKEN *Zeitsch f die ges exp Med*, 1923, *xxvii*, 343
- NICHOLAS AND SWINGLE *J Anat*, 1925, *xxv*, 469
- PALLADIN AND GRILICHE *Biochem Zeitsch* 1924, *cxli*, 450
- PATON, N *Edinburgh Med J*, 1924, *p* 541
- PETTY, O H, STONER, W H, AND SHAFFER, H W Report to the Philadelphia County Med Society, October 28, 1925
- RAYNARD *Comptes rendus des travaux de l'école royale vétérinaire de Lyon pendant l'année scolaire, 1834-35 Rec de med vët Lyon*, 1836, *iii*, 8 Quoted from Sutherland Simpson *Endocrinology and Metabolism* 1922, *i*, 510

- RONA, P, PETOW, H, AND WITTIOWER, E. *Biochem Zeitsch*, 1924, *cl*, 468
- SATVESON, H A. (a) *J Biol Chem*, 1925, *lvi*, 443 (b) *Acta Medica Scandinavica Supplementum*, *vi*, 1923
- SANDSTRÖM, J. *Upsala läkarefor förh*, 1880, *xv*, 44
- SCHIFF, J M. (a) *Untersuchungen über die Zuckerbildung auf die Erzeugung* Würtzburg, 1895, Stohel *vi*, 156 (b) *Aub f exper Path u Pharm Leipzig*, 1884, *xviii*, 25 (c) *Rev med de la Suisse rom Geneva*, 1884. Quoted from *Endocrinology and Metabolism*, *vol 1*, 425
- SCOTT, H H. *Lancet*, 1925, *i*, 620
- SNELL, J. *Amer Med Assoc*, 1925
- THLESTON, W. Quoted by Palmer W W and Van Slyke, D D, *J Biol Chem*, 1917, *xxxii*, 499
- TOGAWA, —. *J Lab and Clin Med*, 1920, *v*, 299
- UNDERHILL, F P, AND BLATTERWICK, N R. (a) *J Biol Chem*, 1914, *xviii*, 87 (b) *J Biol Chem*, 1914, *xix*, 119
- VASSALE, G. (a) *Arch ital de Biol*, 1898, *xxx* (b) *Arch ital de Biol*, 1905, *xliii*, 177
- VASSALE, G, AND GENERALI, F. *Arch ital de Biol*, 1900, *xxxiii*, 154
- VINCENT, S, AND JOLLY, W A. *J Physiol*, 1905, *xxxii*, 65. *J Physiol*, 1906, *xxxi*, 295 and 305
- VINES, H W C. (a) *J Physiol*, 1921, *lv*, 209 (b) *Brit Med Journ*, 1923, *ii*, 559
- WATANABE, C K. *J Biol Chem*, 1918, *xxxvi*, 531
- WHITT, F D, AND CAMERON, A T. *Trans Roy Soc Can*, 1925, *xix*, Sect V, 45
- WILSON, D W, STERNS, T, AND THURLOW, M. *J Biol Chem*, 1915, *xxiii*, 89



## PRESENT KNOWLEDGE OF FILTERABLE VIRUSES

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As all have realized in attempting to review this obscure subject the first difficulty lies in deciding what diseases are to be considered. Any survey of the progress of our knowledge through the last forty or fifty years will show that during this time we have made enormous strides in emerging from that rather cloudy state of ignorance which prevails when we have succeeded in delimiting diseases merely on the basis of their clinical course even when supported by a knowledge of their pathological anatomy. This progress is due in each instance to the recognition of the aetiological factor and in the case of an infectious disease we must not only see the living cause of the disease but we must learn its zoological or botanical relations and its whole life history. In the course of these years we have learned all this about a host of bacterial and protozoan infections and have come to understand completely the part played by more highly organized animal and plant parasites.

More recently we have realized that there are other groups of organisms which live as parasites and cause disease, but of the systematic position and of the life history of these we are less well informed. Such are the spirochaetes which we cannot yet classify with absolute certainty either with lowly plant or animal forms. While we know a great deal about the life history of some of them, we are still much in the dark about others and it is a little disturbing to find that some are transmitted by ticks or mosquitoes while others are not dependent upon such carriers. It does not seem probable that any essential part of the cycle of their development takes place in these intermediate hosts but rather that they are mechanically transferred much as the plague bacillus is transferred by fleas. At this point it may be said that the part played by such insect carriers seems to be different in different diseases and it is impossible to con-

clude from the knowledge that a certain disease, such as dengue, is transmitted by mosquitoes, that it is caused by a protozoan or a spirochaete. The precise relation of many of these organisms to their intermediate hosts or carriers remains to be worked out.

Another group of organisms which we are only beginning to know is that of the Rickettsias. These minute granule-like bodies occurring often in great masses within cells, often extracellular, are usually parasites or commensals in insects. Their systematic relations are by no means established and little is known of their life history. They do not pass through a filter but are transmitted to man and animals by their insect host, causing such diseases as typhus fever. A third group also of minute granule-like organisms which will only exceptionally pass through a filter and of which we know nothing more as regards the life history, is recognized only because they cause such diseases as smallpox.

After this it becomes exceedingly difficult to group together on any rational basis the aetiological agents of the many remaining infectious diseases of which we have a still more unsatisfactory knowledge.

Most of these diseases seem to be caused by some living creature so small as to pass readily through a porcelain filter which will hold back bacteria and other relatively bulky organisms. They must be very small but it is impossible to think of filterability through a Berkefeld or Chamberland filter as a satisfactory basis for classification so that the title of this paper becomes misleading. For no two filters are equally permeable, and many external circumstances modify their permeability. Pressure, the degree of dilution of the fluid to be filtered, its viscosity, the presence of viscous sediments which may clog the filter, the possible existence of various stages in the development of the organism with corresponding differences in size and consistency,—all these things affect the passage of organisms. Indeed, Dr Holman has shown that the slightest smearing of a filter with oil will make it permeable. All this is of great interest in the case of such organisms as pass with difficulty through filters—for example, those of smallpox and vaccinia which seem to have been driven through filters by some investigators although it was evident that but few of them went through and only when the material was greatly diluted and freed of viscous impurities.

On the other hand there are many diseases the living virus of which passes readily and in full strength through every kind of porcelain filter. Of these there are some in which it is easy to demonstrate this fact because the disease can readily be reproduced by the inoculation of the clear filtrate but there are others, severe or fatal diseases of human beings, which have every appearance of being of the same nature in which filterability of the virus has not been demonstrated probably because no other animals are susceptible and no one has ventured to inoculate human beings. Rheumatism is apparently such a disease.

The list of these diseases is a rather long one and one group seems to be set apart because of the predominant involvement of the central nervous system in which there are produced profound destructive changes. This group includes poliomyelitis, encephalitis lethargica, herpes, rabies, distemper of dogs and probably other diseases such as Borna's disease of horses. But in spite of the similarity of the pathological changes, it is by no means certain that the causative agents are intimately related.

We have no good basis for grouping such diseases as equine distemper, African horse sickness, fowl pest, foot and mouth disease, hog-cholera, rinderpest, influenza, mosaic disease of tobacco and other plants, infectious anaemia of horses and infectious leukaemia of fowls, nor do we know where to class the pleuropneumonia of cows and of horses, measles, scarlatina, dengue, rheumatism, verruga, mumps, molluscum contagiosum, warts and trachoma. There are ten or twelve other diseases of local occurrence which are equally difficult to classify although it is known that they are produced by a filterable virus.

In many of the diseases mentioned there are curious inclusions in the affected cells either in the cytoplasm as in smallpox, vaccinia and the related infections and in rabies and trachoma, or in the nucleus as in herpes. Much attention has been concentrated upon these but although their presence is recognized as constant and specific for each disease so that they have a great diagnostic importance, there is no real knowledge of their nature. While some hold them to be a part of the life cycle of the parasite, others maintain as stoutly that they are merely the result of degenerative changes in the cytoplasm or nucleoplasm of the cells.

Morphological studies after all have been of relatively little value in the attempt to unravel the nature of these peculiar diseases. Cultivation of the parasites has almost always failed—the viruses of pleuropneumonia of cattle, poliomyelitis and vaccinia are almost the only exception and in those it has succeeded only after the most extraordinary efforts. Separation of the virus by filtration and the transmission of the disease by inoculation is the main procedure in these investigations and this depends upon the availability of susceptible animals. Of course when the same species can be used it is a simple matter but when the virus must be inoculated into some other animal difficulties are encountered not only because of the new medium in which the character of the virus may suffer a profound change, but because of the confusion often produced by the spontaneous occurrence in the test animal of some other virus, independent, but similar to that inoculated.

The testing of the immune reactions produced in these diseases has frequently thrown light on the specific relation of the virus to the disease although this is usually limited to the observation of the protection of actively and passively immunized animals against the inoculation, and of anaphylactic reactions in immune animals.

Of the whole list, if we except the Rickettsia infections and the smallpox group in which the recognizable infective agents are still on a rather precarious basis, there is not one in which we have satisfying knowledge of the organism and its life cycle. Poliomyelitis is doubtless best known of all—from the work of Flexner, Lewis, Noguchi, Amoss and others it is known that this is a virus which can be inoculated into monkeys, producing the disease and can be isolated in a water-clear filtrate in which nothing can be seen but which is still potent to produce the disease, and can even be cultivated in visible form upon media containing fresh tissue.

Pleuropneumonia of cattle seems to be caused by a minute organism named by Nocard and Roux, *Asterococcus mycoides*, which can be cultivated in various media and will reproduce the disease. But after this in a list of perhaps forty diseases nothing is known of the nature of the organism except that it will go through a filter. It seems a poor record after all these years of effort and in spite of the outpouring of an oppressive amount of literature, that so very little

should be known with certainty Progress has been made in the study of *Rickettsia* infections, of the poliomyelitis-encephalitis-herpes group and to a less extent of the smallpox-vaccinia group, and these we may discuss with some mention of the recent studies of scarlet fever, measles, influenza, rheumatism, etc., among the human diseases

Yellow fever is almost universally regarded as settled in the light of Noguchi's discoveries, but one is still curious about the difficulty in finding the leptospira, its intimate relation with the leptospira icterohaemorrhagica which is so often present in rats in the places where yellow fever is found, and especially about the obligate relation of the infection to one species of mosquito and the period of twelve days which must elapse before the mosquito which has bitten a yellow fever patient can infect another person All of these things seem far more compatible with the idea that yellow fever may be caused by some organism specifically related to the *Stegomyia* and like malaria completing part of its life cycle in the mosquito

#### RICKEITTSIA INFECTIONS

It seems fairly clear from the work of Ricketts, da Rocha Lima, Prowazek, Jungman, Wolbach, Palfrey and Todd, Weigl, Kuczynski, Cowdry, Sellards, Nagayo and others, to mention only the most familiar names, that these peculiar organisms are directly concerned in the production of several diseases *Rickettsia prowazeki*, transmitted by lice, seems to be clearly shown to be the cause of typhus fever, it is an intracellular parasite in the intestinal epithelium of the lice which have fed on a person ill of typhus How it is transmitted to the next person is not clear except that such lice by biting a normal person can transmit the disease whether by the actual bite or by the infection of this puncture wound with their faeces The organism is found in the endothelial cells of capillaries in persons dying of typhus, it is not filterable and has been cultivated only in growing tissue in vitro by Wolbach and in these cultures it survives and multiplies only so long as the tissue remains alive Immunological relations, such as agglutinin formations, are rather specific and protection is obtained in guinea pigs inoculated with *Rickettsia prowazeki* against inoculation of typhus blood



Trench fever, or Wolhynic fever, is apparently caused by another *Rickettsia* which is extracellular in the louse intestine Strong found a filterable virus in cases of trench fever which is opposed to this, but there is much evidence (Bacot, Jungman, Topfer and others) that the presence of *Rickettsia quintana*, or *Wolhynica* or *pediculi* in the body of the lice is a specific result of feeding on trench fever patients and that their infectivity depends on this

Rocky Mountain spotted fever is clearly shown to be due to an allied form, *Dermacentroxenus rickettsi* which is transmitted by a louse, *Dermacentor venustus* The organism is not filterable but has been cultivated or at least maintained in tissue cultures of testes in vitro (Wolbach and Schlesinger)

Cowdry has shown that the heart-water disease in sheep is definitely caused by *Rickettsia ruminantium* which is transmitted by *Amblyomma hebraeum* (a tick), and quite recently Sellards, Nagayo and others have found a *Rickettsia* in Tsutsugamushi disease which is pathogenic for guinea pigs and monkeys and transmitted by the mite *Trombicula akamushi*

On the whole it appears that we may regard this as a group of infections, not, it is true, caused by a filterable virus but difficult of study and obscure, and therefore mentioned here because this is practically the definition of our subject rather than filterability It is good that such satisfactory progress has been made in clearing up these diseases and with these examples before us there seems little doubt that the further exploration of the relations of this type of organism which seems to be widely represented in insects at least, may be fruitful and relatively easy

#### THE SMALLPOX-VACCINIA GROUP

Although, of course, these diseases have been practically well known for ages and are readily transferable and have furnished us with our first classical idea of artificial immunity, the nature and life history of the organisms are but little understood That the organisms are very minute is well known, that they are really readily filterable is very doubtful Some authors have succeeded in driving vaccine through filters—others have failed, and in the most successful attempts the quantity of the virulent material has been greatly reduced The

organism of vaccinia has been cultivated in living tissue cultures *in vitro* but not otherwise. Its increase has been shown by the more profuse effects upon animals (Steinhardt and Lambert), or by the calculation of dilution and time of maintenance. It is evident that if a tissue culture inoculated with a minimal amount of vaccine, perhaps even less than is necessary to infect a rabbit's cornea, is transferred many times throughout a long period in the incubator which would in itself be enough to kill the virus, and is then found abundantly able to infect the rabbit's cornea, the virus must have increased greatly (Parker and others). Prowazek, Aragao and Beaurepaire, Paschen, Gins and many others have recognized minute granules in vaccine and all have observed the inclusions (Guarnieri bodies) in the epithelial cells. MacCallum and Oppenheimer have separated the granules from the rest of the vaccine by differential centrifugalization and in work now going on Oppenheimer has washed these granules free of all adherent material and found them infective and Craciun and Oppenheimer have been able to cultivate the washed granules in tissue cultures for many generations.

Doubtless all this will hold true for the closely allied affections—the milder forms of variola, alastrim, etc., horsepox, goatpox, swinepox, sheepox, which seems of all these the most independent disease, and finally the fowlpox or epithelioma contagiosum of fowls. But it leaves us ignorant of the systematic position of these minute granules and of most of their life history, even of their relation to the cellular inclusions which are so characteristic. Nevertheless, the progress of late years is very definite and promises rapid advances in the near future. Varicella, or chickenpox, has always been ranged with these diseases and it is quite possible that it belongs here although as will be related, attempts have recently been made to align it with another group—that of herpes.

#### POLIOMYELITIS, ENCEPHALITIS, HERPES GROUP

The most intense interest has been concentrated upon these diseases recently because of their wide and fatal epidemic occurrence. The study of poliomyelitis is now set aside as practically completed and little new work has appeared in recent years. The main points have already been referred to and it seems that with practically com-

plete knowledge of the clinical symptoms and the anatomical changes, and with the demonstration of a filterable virus capable of reproducing identical conditions in monkeys and of being cultivated in artificial media, the comprehension of the disease should be satisfactory. But we cannot see the organism ordinarily, except in the form of globoid bodies in incubated tissues and in cultures and since we know little of the relation between these granules and the invisible virus in the water clear filtrate which is yet so potent, it can hardly be said that we understand the life history of this organism. But then we might say that it is possible that we are equally in the dark about the whole life history of the most familiar pathogenic bacteria.

With regard to encephalitis lethargica we now know well the clinical course and the pathological anatomy but we are entirely ignorant of the nature of the causative agent. It is true that various authors have announced the discovery of a virus which can be transmitted to animals such as rabbits, but the evidence is unsatisfactory. Strauss, Hirschfeld and Loewe transmitted the disease to rabbits very readily and were supported by Thalhimer. Levaditi and his coworkers also succeeded in producing encephalitis in one rabbit by inoculating material from the brain of a person dead of encephalitis and in another by inoculating nasal washings, and all their subsequent work has been with these two viruses. Doerr and his associates have secured another virus in the same way. But all of these are open to criticism chiefly on account of the discovery by Gruter, Loewenstein and others that the virus of herpes simplex is very readily inoculated into rabbits and produces in them a fatal encephalitis. This has been confirmed and studied by so many investigators that it is perfectly established and Lipschutz has described a specific intranuclear inclusion which is characteristic of herpes lesions. There is no difficulty in transmitting herpes to rabbits, but enormous difficulty in transmitting encephalitis lethargica. Some writers, such as Bastai and Busacca, even find the herpes virus in the blood and cerebrospinal fluid of persons who are subject to herpes but are at the time in an interval without any actual herpes, and say that in such people any slight disturbance is capable of producing a local herpetic skin lesion. This is denied by Lipschutz but it is at least enough to suggest that persons with encephalitis might sometimes harbor the virus of herpes which

would account for the rare examples of successful inoculation of rabbits

The course of herpes simplex infection has been minutely and satisfactorily studied by Goodpasture and Teague who show that the virus wanders rapidly along the nerves, choosing as its path the axis cylinders and kept in place by the myelin sheaths, spreads out only upon reaching a ganglion or the central nervous system. Short of a knowledge of the morphology and life cycle of the herpes virus, this seems fairly satisfactory but the easy recovery of this virus from occasional non-encephalitic cases such as that of Flexner and Amoss, and the extraordinary difference between the curves showing the effect of inoculation of encephalitis material on the one hand and of herpes material on the other, into rabbits (Ford and Amoss), make one suspect very strongly that all of the so-called viruses of encephalitis are really accidentally recovered herpes virus. This seems a far safer conclusion than that ventured by some that the viruses of encephalitis and herpes are identical, and it is preferable to concede that as yet we know nothing of the cause of encephalitis. All of this has been clearly brought out by Flexner.

In the course of all this groping toward the herpes virus and that of encephalitis, great confusion has been introduced by finding in the rabbit, the common experimental animal in every laboratory, a spontaneous infection which causes a sort of encephalitis. Many have now written descriptions of this organism which is very common in rabbits and which has been classed as a form of microsporidium. Except that it must be recognized to avoid confusion, it has no further interest here. Levaditi has named it *Encephalitozoon cuniculi*.

Nearly related to herpes simplex in our minds is herpes zoster, and beginning with the paper of Bokay there has sprung up the idea that this too may be a transmissible disease produced by a filterable virus and also affecting the nerve and related ganglion. Such an idea is in every way acceptable although combated by many clinicians who feel sure that herpes zoster arises as a secondary effect after many diseases (Comby). It is extremely difficult to transmit herpes zoster to animals although a few, such as Lipschutz, Marinesco and Draganenco, report positive results. Luger and Lauda thought they produced herpes simplex encephalitis by inoculating herpes zoster material and

Cole and Kuttner in their recent studies were quite unable to transfer herpes zoster at all. At least it seems immeasurably more difficult to transmit to animals the virus of herpes zoster than that of herpes simplex and it is doubtful that it has ever been done—once more because of the chance of the accidental presence of herpes simplex virus which might give an illusory success. But the most interesting thing is that Bokay thought that inoculation of herpes zoster might be followed by the development of varicella or chickenpox and vice versa. This has been discussed by a great many, especially in France where Netter and Urbain stoutly maintain that varicella and herpes zoster are only different expressions of the same infection. Clinicians such as Comby are equally forceful in maintaining the complete independence of the two diseases. Lipschutz and Kundratitz have, they say, transmitted herpes zoster to children in whom it often spreads into a general vesicular eruption like chickenpox, easily transmitted to other children by contact as chickenpox. Children who have had varicella are refractory to the inoculation, and those who have been successfully inoculated are immune from chickenpox. Even the serum of convalescents from herpes zoster is said to be protective against varicella. But Lauda and Silberstern deny this and fail to confirm the cross complement deviations of Netter with the serum of zoster patients and varicella antigen.

From all this it is difficult to draw any certain conclusions. It seems quite clear that herpes simplex is caused by a definite filterable virus transferable to rabbits in which it produces fatal encephalitis, and there are suggestive fragments of evidence that it is very widespread and may even exist coincidentally with other infections, and thus lead to confusion when susceptible animals are inoculated from encephalitis or other diseases. But it is by no means easy to feel convinced by any of the experimental studies which appear to demonstrate the causative agent of encephalitis lethargica. Whether herpes zoster is a separate disease caused by a virus distinct from that of herpes simplex is quite uncertain but it seems to be so because it is so difficult to transmit it to rabbits which are so susceptible to infection with herpes simplex. That it has any special relation to chickenpox rests almost entirely on circumstantial evidence and seems at least improbable. But none of this complex field is ripe for discussion and we must await the results of much more experimental study.

In this group there belong perhaps the enzootic encephalitis of horses (Borna's disease), described by Moussu and Marchand as caused by a filterable virus infective for the rabbit and producing in that animal as well as in the horse, a fatal encephalitis. Whether distemper in dogs with its well recognized lesions in the central nervous system is due to such a virus or really to the filterable bacillus bronchisepticus remains an open question (Roman and Lapp).

It may perhaps seem strange and improper to group rabies with this class of diseases too, but in its general behavior it seems to me closely related. Nothing new has been discovered about rabies unless it be the suggestion of Manouelian and Viala that the Negri bodies represent a stage in the cycle of a microsporidian analogous to that described by Levaditi as *Encephalitozoon cuniculi*.

#### OTHER DISEASES CAUSED BY FILTERABLE VIRUSES

Of all the other diseases caused by filterable viruses we are almost entirely in the dark, and it will be tedious to mention them all merely to repeat this statement. However, there is a little light appearing with regard to some of them and at least the promise of better understanding in other cases.

Thus, in the case of common colds, it seems satisfactorily shown by the work of Kruse, Foster, Olitzky and McCartney that bacteria can be excluded by filtration and that a cold may be transmitted by the clear filtrate of nasal secretions from a person in the early stage of a coryza which has been contracted by contact. But that is all and it is only because this is a common disease which affects us all that this information is any more interesting than the similar information which is all we possess concerning certain diseases of horses, such as aphthous stomatitis, equine distemper, pleuropneumonia, African horse sickness, and infectious anaemia, or certain diseases of cattle such as foot and mouth disease, rinderpest, stomatitis papulosa and agalaktia contagiosa. Other similar diseases affect swine—hog cholera, or sheep, catarrhal fever, Nairobi sheep disease, or fowls, fowlpest, infectious leukaemia of hens, etc. There are other diseases still, affecting rats and guinea pigs, rabbits, birds, silkworms, etc., and doubtless a host of others which we have never noticed. Great excitement was aroused by the statements of Trosch and

Dahmen that they had discovered the cause of foot and mouth disease by photography by ultraviolet light, but this is left to lapse into silence by the commission of the German Microbiological Association appointed to investigate it and similar skepticism seems to prevail with regard to the analogous discovery by Barnard of the cancer parasite by the same method. But there still remain several human diseases of great importance which have not exactly fallen into any of these classes although they seem to be closely related usually because they behave like those which are due to a filterable virus. Such are influenza, measles, scarlatina, dengue, pappataci fever, rheumatism, verruga and after these the local affections, molluscum contagiosum, warts and trachoma.

As to *influenza*, the efforts of almost all the workers in the world failed to discover the etiological factor when the most gigantic material was offered but at least the impression became general that the bacillus of Pfeiffer could claim nothing more than the rôle of a secondary invader and that there must be a filterable virus although no one could demonstrate it. The work of Olitzky and Gates on the *Bacillus pneumosintes*, a filterable bacterium, is extremely interesting but does not convince one at once that in that organism the cause of the epidemic is found. No one has actually reproduced the disease in characteristic form in spite of many efforts and it remains an unsolved problem.

*Measles* studied by the usual methods has shown itself to be a disease caused by a specific virus which is found in the blood, nasal and conjunctival secretions, and elsewhere in the body. It will pass through a porcelain filter and will reproduce the disease when injected into susceptible human beings or monkeys. Hektoen demonstrated this clearly and his results were confirmed by Goldberger and Anderson and later by Blake and Trask, although Sellards had arrived at an opposite conclusion. Others have described similar infection of rabbits and guinea pigs (Nevin and Betman, Duval and D'Aunoy), but whether these are convincing or not there seems little doubt about the fact that man and monkeys can be thus infected. None of these experiments resulted in any demonstration of a visible organism although Mallory described minute bodies in the endothelial cells of capillaries in the exanthem. Recently Caronia and Sindoni

have found in the blood, bone-marrow, filtrate from nasal secretions and cerebrospinal fluid of infants in the prodromal or exanthematic stage of measles, an organism which grows anaerobically in catalytic media and which is visible as very minute granules in pairs. This organism will pass through a porcelain filter and from the clear filtrate new cultures may be made. Inoculation of large doses of the culture intravenously produces a disease like measles in rabbits and the organisms may be recovered. The serum of children convalescent from measles specifically agglutinates these organisms. Inoculation of inactivated or attenuated cultures produces immunity from measles in children while large doses of the living culture produce typical measles. de Villa has shown that inactivated cultures injected into the skin produce a reaction like the Schick reaction in non-immunes but not in immune persons. Various others have found the organism (Arloing and Dufourt, Ritosso, etc.), and Dr Saphro is now working with it in our laboratory. She has succeeded in cultivating it from cases of measles and although we have seen that it corresponds in its morphological and cultural characters with the cultures brought from Caronia's laboratory, we must await further study.

*Dengue*, which resembles measles in some respects, has been shown by Graham, Ashburn and Craig, Cleland, Bradley and McDonald and others to be transmissible to human beings by inoculation of blood even when filtered through a porcelain filter. The organism is thought by Chandler and Rice not to be a spirochaete although some authors have suggested this. Graham thought it an amoeboid body within the red corpuscles but no one has confirmed this. Duval and Harris think they have transmitted the disease to guinea pigs as shown by fever, fall in leucocytes and enlargement of the spleen and have cultivated certain globoid bodies for many generations which will produce the same results when inoculated into guinea pigs. Great interest centres in the relations with mosquitoes which naturally transmit the disease. While Graham and Ashburn and Craig thought that *Culex fatigans* or *quinquefasciatus* was the natural carrier, Bancroft, Cleland, Bradley and McDonald, Chandler and Rice, and most recently Siler, Hall and Hitchens have shown that the *Stegomyia fasciata* (*Aedes aegypti*) is really the vector and not *Culex fatigans*. The latter group of authors show that mosquitoes can



receive the virus from patients in the first, second and third day of the disease, that the virus must remain in the mosquito eleven days before transmission is possible. Immunity follows the disease but is not absolute and most persons who live in countries where dengue is common go through several attacks in successive years, the illness becoming milder each time until they seem to be quite immune. From this we may conclude that the organism has yet to be discovered but that like that of malaria it seems to require time to complete some part of its life cycle in the mosquito. This, of course, is not a strict consequence but otherwise it is difficult to explain the eleven day period unless we merely assume that the organism grows in the mosquito until the dosage becomes sufficient to produce infection. It would be interesting to determine whether one mosquito after eleven days could infect several persons.

Of *scarlet fever* there is little to say here. De Cristina, Caronia and his associates, and others have found an organism like that described in measles but others who have attempted to repeat this work have failed to confirm it (Burgers and Bachmann, Meyer). It has, of course, always been traditionally held that scarlet fever is an exanthematic disease closely related to such diseases as measles and leaving behind it a lasting immunity, but generally complicated by a secondary infection with streptococci. The immunity and various anatomical changes seemed characteristic of scarlet fever in contrast with what is found in uncomplicated cases of streptococcal infection. Now it appears from the work of Dochez and of Dick and Dick that a special streptococcus is concerned, that this as Dochez says is constantly associated with the primary and secondary manifestations of the disease, it is specific in character, able to produce the experimental disease in man and animals, its toxic effects are neutralized by the serum of human convalescents. On the other hand the specific toxic phenomena of scarlet fever in man can be made to disappear by an antitoxic serum produced in the horse by this streptococcus, and a Berkefeld filtrate from cultures of the organism is found to contain a toxin which is specifically related to immunity in scarlet fever as shown by skin tests. From all this Dochez concludes that the *Streptococcus scarlatinae* is the principal and probably the only aetiological agent of scarlet fever.

*Pappataci fever* or phlebotomus or three day fever, which is so widely distributed in the tropical and Mediterranean countries, was shown by Doerr and Russ and Birt to be due to some filterable virus which circulates in the blood and which upon injection into susceptible persons will produce the disease. It is transmitted by a sort of mosquito, the pappataci (*Phlebotomus papatasi*) which is able to infect another person only after the virus has been in its body for seven days, which again suggests that some part of the life cycle of the organism must take place in the vector's body. Nothing satisfactory has been done in the way of recognizing precisely this organism. Whittingham thinks it may be a leptospira but it is not pathogenic for guinea pigs and not inherited by the phlebotomus.

*Rheumatism* is quite clearly an acute and recurring specific infectious disease producing absolutely peculiar and characteristic anatomical changes. No bacteria have been satisfactorily recognized as the causative agent and in spite of many attempts no one has succeeded in producing the disease experimentally in any animal. As far as recorded no one has attempted to infect a human being with this extremely serious disease, and although it seems possible that it may be due to a filterable virus, there is no evidence upon which to base any statement.

*Verruga peruviana*. No perfectly clear idea of the aetiology of this disease is yet available in spite of the considerable amount of attention recently paid it. The general opinion which prevails among the investigators in Peru is that Oroya fever in which peculiar minute bacillus like organisms are found in the red blood corpuscles (*Bartonella*) is the first stage in a disease in which later the nodules or verrugae appear on the skin and elsewhere. Strong and his associates, however, believe that the Oroya fever and verruga are separate diseases. They could not transmit Oroya fever to animals but could inoculate monkeys and other animals with verruga although they could not demonstrate a filterable virus nor any definitely visible organism.

As to common warts, Jadassohn was able to transmit them by inoculation. Cuffio could filter the material and still produce them by inoculation and Wile and Kingery have not only reproduced them in human beings by filtrates but have transmitted them in the same way to a second generation. In all cases the period of incubation from the time of inoculation to the development of the warts is very long.

*Molluscum contagiosum* is another disease of human beings which has been reproduced in typical form by the injection of a bacteria free filtrate probably by Juliusberg, certainly by Wile and Kingery. The cellular inclusions are typical but the organism is evidently an extremely minute form. The relation of this to the epithelioma contagiosum of fowls is not settled. That disease which sometimes appears as a diphtheritic inflammation has been mentioned already in relation with vaccinia. It has been shown by Marx and Sticker to be transmissible by the injection of a filtrate and in the emulsion there are found minute granules somewhat like those found in vaccinia.

Nothing new seems to have been accomplished in relation with the various other less-known diseases due to filterable viruses except that Olitzky in working with the virus of mosaic disease of tobacco has been able to cultivate it in a medium made from the plant and to show by calculating the dilution that the invisible virus must have multiplied greatly.

One is left with the feeling that in comparison with the amount of work, and especially with the bulk of the publications in this field, very little has been accomplished. The question arises as to what we really want to know about these viruses and it seems that this may be answered from two points of view. As a matter of intellectual interest we want to know their morphology, their behavior with regard to various environmental conditions, and particularly their whole life history. If we could know the life cycle of any organism, even including the common bacteria, with such precision as we know that of the Schistosomes or of malaria, we would feel content. As a matter of practical interest merely to enable us to combat the disease we might be quite content to know only that this is a filterable virus and that somewhere in its life history there is a point at which its transmission can be attacked as is the case with yellow fever. Even if we doubt the part played by the *Leptospira*, we know that the virus must be carried by the *Stegomyia* and it is only necessary to keep this pest from biting the persons who have the disease to exterminate the disease. From this practical point of view immunological relations assume an importance far out of proportion to their interest from the other standpoint, and practically we can control the spread of many of these diseases or prevent their occurrence in an individual.

One has the impression that progress is slow because we still use blindly the methods of investigation which have been worked out with such effort for bacteria. When someone succeeds in devising new conceptions—as new as the use of aniline dyes and solid media were for the early days of bacteriology, progress may be rapid. It seems far from impossible that totally different media may be necessary for the cultivation of these minute organisms and that quite different principles of immunity may prevail. One organism properly worked out should serve as a model for all the rest. It is intriguing to reflect that while we know of the existence of only those filterable viruses which produce disease, there are doubtless thousands of such minute living creatures round about us which will forever escape our perception.

## LITERATURE

*Rickettsia infections*

- ABE *Ctbl f Bakt u Par*, 1, 1923-24, Ong, xci, 217  
 ARKRIGHT *J Roy Army Med Corps, Lond*, 1924, xlii, 447  
 BREINL *Ztsch f Immunitätsforsch*, 1924, vi, 486, *Journ Inf Dis*, 1924, xxxiv, 1, *Med Klinik*, 1924, x, 118  
 CONNOR *Journ Inf Dis*, 1924, xxxv, 387  
 COWDRY *Journ Exp Med*, 1925, xlii, 231, 253  
 FEJGIN *Comptes rendus soc de biologie*, 1924, xcl, 976  
 HAUDUROU *Progres med Paris*, 1923, 3s, xxxvi, 671  
 KRONTOWSKI AND HACH *Kl Woch*, 1924, iii, 1625  
 KUCZYNSKI, BRANDT AND MASCHUTSCH *Kl Woch*, 1924, iii, 1429  
 NAGAYO AND OTHERS *Sc Rep Govt Inst Inf Dis Tokyo*, 1924, iii, 37  
 NOGUCHI *Journ Exp Med*, 1923, xxxviii, 605  
 DA ROCHA LIMA *Lubarsch u Ostertag, Ergebnisse d allg Path*, 1923-24, xx, 2  
 SELLARDS *Am Journ Trop Med*, 1923, iii, 529  
 SIKORA *Kl Woch*, 1924, iii, 2008  
 WFIGL *Kl Woch*, 1924, iii, 1590, 1636  
 WEIL, BREINL UND GRUSCHKA *Zts f Immunitätsforsch*, 1923, xxviii, 447  
 WOLBACH, TODD AND PALFREY *Etiology of Typhus Fever*, Harvard Univ Press, 1922  
 WOLBACH *Journ Am Med Assoc*, 1925, lxxxv, 723  
 WOLBACH AND SCHLESINGER *Journ Med Research*, 1923-24, xlv, 231  
 WOODCOCK *Journ Roy Army Med Corps, Lond*, 1924, xlii, 121

*Smallpox vaccinia group*

- BLANC ET CAMPOPETROS *C R Soc de Biol*, 1923, lxxviii, 1020, lxxxix, 38  
 CAMLS *Bull de l'Acad de Med*, 1923, vi, 79  
 GINS *Zts f Hyg u Infektionskr*, 1924, ciii, 281  
 GOERTTLER *Zts f Immunitätsforsch*, 1923-24, xxxviii, 357

- GORDON Med Research Council, Special Report, No 98, 1925  
 KRUMBACH Zts f Immunitätsforsch, 1923-24, xxxviii, 1  
 LEVADITI ET NICOLAU C r Soc de biol, 1921, lxxxv, 345, 1923, lxxxviii, 571, 1923, lxxxix, 484, Annales Inst Pasteur, 1923, xxxvii, 1.  
 LUCKSCH Ctbl f Bakt u Par, i, 1925, Orig, xcvi, 309  
 NAKAGAWA Zts f Immunitätsforsch, 1925, xlii, 409  
 NODAKE Ibid, 1924, xli, 52  
 PARKER Journ Med Research, 1923-24, xlii, 645  
 PARKER AND NYE Am Journ Pathology, 1925, i, 325  
 POPPI UND HERZBERG Ctbl f Bakt u Par, i, 1925, Orig, xcvi, 211.  
 SCHNEIDER Zts f Immunitätsforsch, 1923-24, xxxviii, 271  
 v SCHUTZ Zts f Hyg u Infektionskr, 1925, cv, 1.

*Polymyelitis-encephalitis-herpes group*

- AVIRAGUET, HUBER ET DAYRAS Bull et mem soc d hop Paris, 1925, 3s, xlix, 185  
 BASTAI UND BUSACCA Klin Woch, 1924, iii, 147, 442  
 BLANC ET CAMINOPETROS C r soc biol, 1921, lxxxiv, 629, 767, Ann Inst Pasteur, 1924, xxxviii, 152  
 BOKAY Jahrb f Kinderheilk, 1924, cv, 8  
 COMBY Bull et mem soc d hop Paris, 1925, 3s, xlix, 187  
 COLE AND KUTTNER Journ Exp Med, 1925, xlii, 799  
 DOERR UND SCHNABEL Zts f Hyg u Inf, 1921, xciv, 29  
 DOERR UND ZDANSKY Ibid, 1924, cii, 1  
 FLENER Journ Am Med Assoc, 1923, lxxxii, 1688, 1785  
 FLENER AND AMOSS Journ Exp Med, 1925, xli, 215, 233, 357  
 FORD AND AMOSS Bull Johns Hopkins Hosp, 1924, xxxv, 20  
 GOODPASTURE Amer Journ Pathology, 1925, i, 1  
 GOODPASTURE AND TEAGUE Journ Med Research, 1923-24, xlii, 121.  
 GILDEMEISTER UND HERZBERG Dtsch med Woch, 1925, li, 97.  
 GRÜTER Munch med Woch, 1924, lxxi, 1058  
 HOFF, OREL UND SILBERSTEIN Zts f d ges exp Med, 1924-25, xlii, 257.  
 KORITSCHONER Virch Arch, 1925, cclv, 172  
 KLING, DAVIDE UND LILJENQUIST C r soc de biol, 1924, xc, 507, 511, 514  
 KUNDRATITZ Monats f Kinderh, 1924-25, xxix, 516  
 LAUDA Ctbl f Bakt u Par, i, 1924, xci, Orig, 159, 205  
 LAUDA UND SILBERSTEIN Klin Woch, 1925, iv, 1871  
 LUGER UND LAUDA Wien kl Woch, 1925, xxxviii, 33, Klin Woch, 1925, iv, 209,  
 Zts f d ges exp Med, 1924, xxxix, 1, Klin Woch, 1924, iii, 1507, 2309,  
 Zts f Hyg u Infektionskr, 1923-24, ci, 424  
 LEVADITI Paris medicale, 1925, lv, 573  
 LEVADITI, HARVIER ET NICOLAU C r soc de biol, 1921, lxxxv, 161, 213, 287, 1923, lxxxix, 984, 1924, xc, 1372, Ann Inst Pasteur, 1922, xxxvi, 63, C r Acad d Sc, 1923, clxxxvii, 985  
 LEVADITI, NICOLAU ET SCHOEN Ann Inst Pasteur, 1924, xxxviii, 651  
 LIPSCHÜTZ Ctbl f Bakt u Par, i, 1924, Orig, xciii, 361, Wien kl Woch, 1924, xxxvii, 183, 1925, xxxviii, 89, Arch f Dermatol u Syph, 1921, cxxxvi, 479, 1925, cxlii, 196, 379  
 LIPSCHÜTZ UND KUNDRATITZ Wien kl Woch, 1925, xxxviii, 499, Klin Woch, 1925, iv, 998

- MARINESCO ET DRAGANESCO *Ann Inst Pasteur*, 1923, xxxvii, 753  
 MCINTOSH AND TURNBULL *Brit Journ Exp Pathol*, 1920, i, no 2  
 MOUSSU ET MARCHAND *Encephalite enzootique du cheval*, Paris, 1924  
 MCCARTNEY *Brit Med Journ*, 1924, ii, 1159, *Journ Exp Med*, 1924, xxxix, 533  
 MARIANI *Arch f Dermat u Syph*, 1924, cxlvii, 259  
 NETTER *Bull et mem soc d hop Paris*, 1925, 3s, xlix, 192, 249, 321, 998  
 NICOLAU ET POINCELOUX *C r soc de biol*, 1923, lxxxix, 779, 1924, xci, 1063, *Ann Inst Pasteur*, 1924, xxxviii, 977  
 PARKER AND NYE *Amer Journ Pathol*, 1925, i, 337  
 PARKER *Journ Med Research*, 1923-24, xlv, 289  
 PERDRAU *Brit Journ Exp Pathol*, 1925, vi, 123  
 ROUSSEAU *Progr Med Paris*, 1924, xxxv, 725  
 SCHNABEL *Klin Woch*, 1923, ii, 429, 1924, iii, 1015, *Wien klin Woch*, 1923, xxxvi, 84  
 STRAUSS, HIRSCHFELD AND LOEWI *Journ Infect Dis*, 1919, xxi, 378, 1920, xxvii, 250, *N York M Journ*, 1919, cix, 772  
 TRAHNER *Archives of Neurology and Psychiatry*, 1924, xii, 73  
 WOODCOCK *J Roy Army Med Corps*, 1925, xlv, 45

#### *Rabies*

- CARONIA E SINDONI *Pediatna*, 1924, xxxii, 817  
 IMAMURA *Mitth a d med Fakult d k Univ Tokyo*, 1922, xxix, 307, 347  
 LEVADITI, NICOLAU ET SCHOEN *C r soc de biol*, 1924, xc, 398, 994, 1924, xci, 56, 423, *C r Acad d Sc*, 1924, clxxviii, 256  
 MANOUVELIAN ET VIALA *C r Acad d Sc*, 1924, clxxvii, 344, *Ann Inst Pasteur*, 1924, xxxviii, 258  
 NICOLLE ET BURNET *C r Soc de biol*, 1921, xc, 366

#### *Dengue*

- ARCHIBALD *Journ Trop Med and Hygiene*, 1917, xx, 133  
 ASHBURN AND CRAIG *Philippine Journ Science*, 1907, ii, 93  
 BANCROFT *Austral Med Gaz*, 1906, xvi  
 CHANDLER AND RICE *Am Journ Trop Med*, 1923, iii, 233  
 CLELAND, BRADLEY AND McDONALD *Journ of Hygiene*, 1918, xvi, 317, 1919, xviii, 217  
 CRAIG *Journ Am Med Assoc*, 1920, lxxv, 1171  
 GRAHAM *Journ Trop Med*, 1903, vi, 209  
 DUVAL AND HARRIS *Journ Exp Med*, 1924, xl, 817, 835  
 SILVER, HALL AND HICHENS *Journ Am Med Assoc*, 1925, lxxxiv, 1163

#### *Foot pest*

- DOERR UND ZDAISKY *Zts f Hyg u Infektionskr*, 1923-24, ci, 125  
 VERANUS, A MOORE *Cornell Veterinarian*, Ithaca, 1925, xv, 1

#### *Foot and mouth disease*

- GINS *Klin Woch*, 1924, iii, 1135  
 GINS UND KRAUSE *Lubarsch u Ostertag's Ergebn d allg Path*, 1923-24, xx, 2, 805  
 GINS UND FORTNER *Zts f Hyg u Infektionskr*, 1924, ciii, 699  
 FRÖSCH UND DAHMANN *Berl tierarztl Woch*, 1924, xl, 662, *Dtsch tierarztl Woch*, 1924, xxxi, 365, 712, *Lancet*, 1924, i, 1329

PFEILER UND SIMONS Klin Woch , 1925, iv, 253

TITZE Ctbl f Bakt u Par , i, 1925, xciii, Orig , 124, Zts f Infektionskr d Haustiere,  
Berlin, 1924, xxvi, 107.

PFEILER Ctbl f Bakt u Par , i, 1924, xciii, Orig , 124

#### *Scarlatina*

DICK AND DICK Journ Am Med Assoc , 1921, lxxvii, 782, 1923, lxxxi, 1166, 1924,  
lxxxii, 265, 301, 544

DI CRISTINA Pediatria, 1921, xlv, 1923

DOCHEZ Medicine, 1925, iv, 251

BURGERS UND BACHMANN Arch f Hygiene, 1924, xciv, 153

#### *Measles*

ARLOING ET DUFOURT C r Soc de Biol , 1924, xc, 763

BLAKE AND TRASK Journ exp Med , 1921, xxxiii, 385, 413

CARONIA Pediatria, 1921, 1922, 1923, Presse medicale, 1923, xxvi, 877.

COMBY Arch de med enf Paris, 1923, xxvi, 686

GOLDBERGER AND ANDERSON Publ Health Rep , 1911, xvi, 847, Journ Am Med  
Assoc , 1911, lvii, 113

HEKTOEN Journ Inf Dis , 1905, ii, 238

SINDONI Pediatria, 1924, xxxii, 888

SELLARDS Medicine, 1924, iii, 99.

DE VILLA Pediatria, 1924, xxxii, 767.

#### *Mumps*

KERMORGANT Ann Inst. Pasteur, 1925, xxxix, 565

#### *Verruga peruviana*

STRONG AND OTHERS Harvard Expedition to South America, 1913

#### *Warts*

WILE AND KINGERY Journ Am Med Assoc , 1919, lxxiii, 970

KINGERY Ibid , 1921, lxxvi, 440

#### *Molluscum contagiosum*

MARY UND STICKER Dtsch med Woch , 1902, xxviii, 893

WILE AND KINGERY Journ cutan Dis and Syphilis, 1919, xxxvii, 793, Archives of  
Dermatology and Syphilis, 1920, ii, 184

#### *African horse sickness*

THEILER Bull No 19, Dept of Agriculture, Union of S Africa, 1921.

## THE PRESENT STATUS OF OUR KNOWLEDGE OF THE ETIOLOGY OF PELLAGRA<sup>1 2</sup>

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On March 26, 1735, nearly two hundred years ago, a physician, Doctor Gaspar Casal, practicing in the little town of Oviedo, Spain, made some notes on the first of a series of cases of a disease known to him and to the people of the locality as *Mal de la Rosa* (1) That disease we now know as pellagra

Casal described the symptoms, termination and sequelae and discussed the cause, nature and geographic distribution of the disease, but it is Casal's ideas as to the cause which alone interest us at this time He thought that the cause resided in a combination of atmospheric conditions and food, food rendering the body susceptible and the atmosphere through an inherent and "malignant" quality acting as the efficient or precipitating cause of the malady The idea, thus for the first time expressed, that food was etiologically related to pellagra persisted but underwent in the course of time various modifications until the theory was evolved that pellagra is an intoxication resulting from the consumption of spoiled maize With this theory of the etiology of pellagra the names of Sette (2), Balardini (2), Roussell (3), and more particularly that of Lombroso (4) are closely associated

Needless to say, there had not been lacking among the older students some who believed that the disease was a communicable one Such belief, however, had at no time been widely held and it had long been fairly completely dismissed from serious consideration in favor of what had become the authoritative and, in certain countries, the official spoiled-maize theory of Lombroso when Sambon (5), first in

<sup>1</sup> Delamar Lecture delivered before the School of Hygiene, Johns Hopkins University, Baltimore, Md., March 1, 1926

<sup>2</sup> Published with the permission of the Surgeon General



PFEILER UND SIMONS Klin Woch , 1925, iv, 253

TITZE Ctbl f Bakt u Par , i, 1925, xciii, Orig , 124, Zts f Infektionskr d. Haustiere,  
Berlin, 1924, xxvi, 107

PFEILER Ctbl f Bakt u Par , i, 1924, xciii, Orig , 124

#### *Scarlatina*

DICK AND DICK Journ Am Med Assoc , 1921, lxxvii, 782, 1923, lxxvi, 1166, 1924,  
lxxii, 265, 301, 544

DI CRISTINA Pediatria, 1921, xiv, 1923

DOCHEZ Medicine, 1925, iv, 251

BURGERS UND BACHMANN Arch f Hygiene, 1924, xciv, 153

#### *Measles*

ARLOING ET DUFOURT C r Soc de Biol , 1924, xc, 763

BLAKE AND TRASK Journ exp Med , 1921, xxxii, 385, 413

CARONIA Pediatria, 1921, 1922, 1923, Presse medicale, 1923, xxxi, 877.

COMBY Arch de med enf Paris, 1923, xxvi, 686

GOLDBERGER AND ANDERSON Publ Health Rep , 1911, xvi, 847, Journ Am Med.  
Assoc , 1911, lvii, 113

HEKTOEN Journ Inf Dis , 1905, ii, 238

SINDONI Pediatria, 1924, xxii, 888

SELLARDS Medicine, 1924, iii, 99

DE VILLA Pediatria, 1924, xxii, 767

#### *Mumps*

KERMORGANT Ann Inst Pasteur, 1925, xxxix, 565

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WILE AND KINGERY Journ Am Med Assoc , 1919, lxxiii, 970

KINGERY Ibid , 1921, lxxvi, 440

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MARX UND STICKER Dtsch med Woch , 1902, xxviii, 893

WILE AND KINGERY Journ cutan Dis and Syphilis, 1919, xxxvii, 793, Archives of  
Dermatology and Syphilis, 1920, ii, 184

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supported by the results of more extensive studies carried out by later workers (10) If the association with poor sanitary conditions were really significant it would be reasonable to expect that the prevalence of the disease might be reduced or that the disease might even be eradicated by improving sanitary conditions An experiment to test this was actually carried out by Siler, Garrison and MacNeal (11) in a cotton mill village of South Carolina and, as reported by them, with notable success in eradicating the disease There is good reason to believe, however, that these workers fell into error in interpreting the result of the experiment for the prevalence of the disease in the experimental village was later found by workers of the Public Health Service to be quite as high as in some other nearby villages with but the crudest methods of excreta disposal (12) It may be stated in this connection, that while there is no sound evidence that the disease can be prevented by improving sanitary conditions, other evidence of the failure of improved sanitary conditions to control the prevalence of the disease has been reported (13) (14)

Some of those who have regarded the association of the disease with poor sanitary conditions as significant, have reported evidence of the occurrence of contact with a preexisting case in a very high percentage of incident cases (7) (8) (9) (15) and have considered some of this as well high conclusive evidence of infection It would be very instructive to examine this evidence in detail but it must suffice to state, as Vedder (17) and Goldberger and Wheeler (16) have pointed out, that much of it is consistent with the conception of a dietary deficiency and that which is not, is the result of faulty or inadequate methods of investigation and really without significance That "contact" has not the significance that some observers have attributed to it is strongly indicated by its failure to operate under what would seem favorable conditions, as we shall endeavor to make clear presently in another connection

The marked seasonal incidence of pellagra, its seemingly sudden appearance and alleged rapid extension in the United States with its notably higher prevalence in the Southern States represent epidemiological characters that one naturally associates with infectious diseases, so that it is not surprising that these have been cited in support of an infective etiology In doing so, however, it was overlooked

that such characters are not peculiar to infectious diseases. Excellent analogies may be found in the literature of beriberi (18) (19) so that they are, manifestly, equally consistent with a dietary etiology.

The notably higher incidence of the disease in adult women than in men has been cited in support of infection on the ground, presumably, that such difference is inconsistent with a dietary etiology. This is, however, by no means necessarily the case as witness, for example, the great preponderance of endemic goitre in girls as compared with boys of the same age (20). While it must be acknowledged that in the light of present knowledge the peculiarities not only of sex but also of age incidence exhibited by pellagra are not altogether satisfactorily explainable on a dietary basis, they are even less satisfactorily explained on the basis of infection. For to suggest a difference in "resistance," virtually the only explanation that the infectionist can advance, is an explanation that is manifestly equally consistent with the dietary theory and it is itself in need of explanation.

Although a satisfactory explanation on a dietary basis of the phenomenon under consideration can not yet be formulated, a number of factors may, nevertheless, be suggested as possibly contributing to bring it about. Thus it is conceivable that during adult life there may be a quantitative difference between the sexes in physiological requirement of the special dietary factor related to pellagra or there may be a difference in the length of the developmental period of the disease so that what, if not interfered with, would be the longer period of evolution of the disease in the male may be conceived as cut short by seasonal changes in diet which do not come quite soon enough however to benefit the female in the same way. It may be suggested further that the housewife may, and on the basis of every day observation doubtless does in some instances, at least, favor the husband and other wage earning members of the household in matters of diet and, also, that the husband and other wage earning members may in some instances modify their diet advantageously by means of supplementary articles of food secured outside of the household. Finally, there may be mentioned as a possible contributing factor the fact of common observation that the diet of the woman (particularly of the housewife) is more likely to be affected by eccentricities than is that of the man.

Here it may be permissible to suggest that eccentricities in diet probably account for many of the sporadic cases both in the general population and in institutions, particularly institutions for the insane, just as they must account for similar cases of scurvy and of beriberi. This may also explain many, if not all, of the cases in well-to-do individuals although it may be well to point out that it by no means follows that all well-to-do individuals are always provided with a good diet nor that even when so provided that they always eat it. It should not be overlooked that well-to-do people may be food faddists, that they may be parsimonious, or be unfavorably situated with respect to sources of household food supply and, thus, that their diet may be one-sided, restricted and monotonous and possibly faulty in one or more respects (21). So that in studying the dietary relationship of the sporadic case, whether of one occurring in the home or in an institution, the student should not be content with ascertaining the character of the diet available, that is, of the general diet of the household or of the institution, but should strive to determine just what and how much it was that had in fact been eaten by the affected individual. Failure to do this, explains many, if not all, of the cases that have been reported as instances of the occurrence of the disease in spite of a good diet and, thus, as supporting an infective etiology (22).

The fact that the disease occurs in seemingly well-nourished individuals and in nursing infants has also been advanced as an objection to a dietary etiology. It is a sufficient answer to this objection to point to the same occurrence in scurvy and in beriberi.

In the light of the considerations presented it must be clear that the epidemiological and clinical evidence on which the argument for infection has been based either has not the significance that has been attributed to it or is equally consistent with the dietary view.

The argument for infection has not however been based wholly on clinical and epidemiological grounds. A number of workers have advanced either bacteriological (2) or experimental evidence (23) (24) in its support. Of the reports belonging in this category there is only one of sufficient importance to be here considered. This is the report of Harris (24) of New Orleans of having infected two monkeys with pellagra by inoculating a filtrate from pellagrous tissues. Assuming that the diagnosis of pellagra in these animals was correct

there is nothing in the report to show that it was not diet rather than infection that was the responsible factor. But it is by no means certain that the diagnosis was really correct. That it was an error has already been suggested by Funk (25) and is made highly probable, first, by the fact of the frequent occurrence in the monkey of eruptions that so far as may be judged are much like that described and pictured by Harris, second, by the important consideration that neither he (26) nor any other workers (27) have been able to confirm his original results and, third, by the still more important fact that a number of recorded attempts to transmit the disease to the human subject (28) by means of dermal scales, blood, nasopharyngeal secretions, urine and feces from cases of pellagra have been complete failures. The available experimental evidence must be regarded therefore as, on the whole, affording no support for the idea of pellagra as an infection.

It would seem then that, at best, the evidence so far considered either is equally consistent with the dietary hypothesis or actually affords the idea of infection in favor of which it was adduced no real support.

Let us now turn to some observations that, as will be seen, not only afford no support to, but are difficult or impossible to reconcile with an infective etiology. And, first of all, may be cited an observation reported by Kulz (29), an army surgeon with the German army of occupation in Roumania during the World War. He has reported that in spite of the closest contact with the Roumanian population, among whom pellagra was prevalent, the several hundred thousand of the military personnel remained free from this disease although they were not exempt from attack by other endemic maladies, such as malaria, typhus, typhoid and dysentery. He characterized this, and, it would seem, not without warrant, as "evidence of very great weight in support of the argument against infection." In this connection, it is of interest to recall that the food conditions in Europe during the World War have been cited by some observers (30) (43) as well nigh conclusive evidence against the dietary origin of pellagra. These observers seem to argue that inasmuch as the people of Europe, particularly those of certain of the belligerent powers, were on starvation diets and necessarily badly nourished during the war and since there was no pellagra amongst them, diet and malnutrition can have nothing to do

with pellagra So far as concerns the relation of a general malnutrition to pellagra this may be freely granted but it appears to have escaped those who reason in this way that if this argument were really valid as regards diet, it would also disprove the now well established dietary relationship of beriberi for, so far as is known, beriberi was no more prevalent than pellagra under the circumstances mentioned The fallacy of the argument resides, of course, in the assumption that because a disease is the result of a faulty diet any faulty or inadequate diet will bring it about—a wholly unwarranted yet, curiously enough, a very common assumption Evidently then the experience of Europe during the war is not inconsistent with the dietary hypothesis

The experience of the German army of occupation in Roumania, to which reference has been made, in its failure to support the idea of infection is in close harmony with certain older observations the significance of which seems, however, to have escaped or has been misunderstood by the advocates of infection These observations fall into one of two classes of which the first represents the experience of institutions, both special and general hospitals, receiving cases of pellagra for treatment In such institutions physicians, nurses, attendants, etc., in frequent contact with the disease and directly or indirectly with the body discharges of persons sick with it, practically never develop the disease while so employed (31) A recent illustration of this is to be found in the experience of Enright (33) with pellagra in Egypt He states that during the three years that he had dealt with some thousands of cases he was struck by the fact that all the orderlies, including British, Turks, and Germans, in attendance on the patients remained free from the disease While we can not agree with Enright in considering this as proving that the disease is neither infectious nor contagious, his observation is certainly a very striking illustration of at least the failure of "contact" to operate when given what would seem to have been an excellent opportunity to do so

Impressive as such observations are, those of the second class are very much more so This class represents the experience of institutions to which cases of the disease may or may not be admitted but in which it is endemic or has, in some instances, been epidemic, or both Thus, it has repeatedly been observed that employes (nurses, attendants, etc.) resident in such institutions, many of whom come in

frequent association or intimate contact with active cases of the disease or their body discharges, or both, practically never contract the disease while so employed and so residing (31). This exemption, considering the circumstances, is extraordinarily difficult if not altogether impossible to reconcile with a hypothesis of infection. From the point of view of diet, however, an explanation readily suggests itself and, in fact, in the instances studied by us the exemption was consistently associated with what was believed to be a significant difference in diet. It would appear therefore that not only is the idea of infection without unequivocal support but there is important evidence with which it is difficult, if not impossible, to reconcile such idea but which is consistent with and is readily explained on a dietary basis. Clearly, then, the weight of the evidence so far reviewed, favors the dietary etiological view and more than warrants its adoption as a working hypothesis.

Now if this hypothesis is sound and pellagra is really due to a faulty diet, then certain implications which this hypothesis carries with it must also be true.

These are, first, that a difference in diet as between pellagrins and non-pellagrins be demonstrable, second, that the disease must be curable by a proper diet; third, that it must be preventable by such a diet, and, fourth, that it may be experimentally produced by diet.

The demonstration of a difference in diet as between individual pellagrins and non-pellagrins is frequently difficult or impossible particularly in localities in which the disease is endemic. The reason for this difficulty is, in the first place, the fact that we have no means for determining in a particular instance whether the seeming non-pellagrin is really free from the disease. Experience and analogy with other deficiency diseases both teach that in many instances the disease is very probably present but not developed to the point of symptoms. In the second place, our basic knowledge as to the nature of the dietary deficiency and, more particularly, as to the preventive value of different foods or combinations of foods is, as yet, much too meager to permit of reliable judgment in all instances as to the adequacy of a particular diet. This difficulty is enhanced, moreover, by the indefinite character of the information that is ordinarily available with respect to the diet of the individual. At best all that ques-

tioning can ordinarily elicit is a qualitative statement. In exceptional instances only can even a partial quantitative statement be secured. Manifestly therefore the determination of a difference in such circumstances is not to be expected. If, however, the comparison is not between individuals but between groups a significant difference is demonstrable or may reasonably be inferred to exist. Thus in a study by workers of the United States Public Health Service (34) carried out in some cotton mill villages of South Carolina in which the disease was endemic, comparison of diets of non-pellagrous with those of pellagrous households revealed that the pellagrous had a more restricted supply of such foods as milk and fresh meat. Similarly, in institutions in which the disease is endemic although the non-pellagrous class (consisting of officers and employes) may appear to and, perhaps, actually does receive exactly the same food as does the pellagrous (composed of the inmates) an indication of a difference in the diet of the two exists in this—that those of the unaffected class, being the officers and employes, are in a position both to serve themselves more liberally of the more desirable articles of the ration and to supplement the institution diet with articles of food or with meals secured outside.

Difficult as it may be to discern any difference in the individual diet in pellagrous households in an endemic locality, indications of a difference can very frequently be discovered in sporadic cases particularly in such as occur in well-to-do persons.

Examples of such cases may be found scattered in the literature. Particularly interesting are some of the cases reported by Vedder (17), Roberts (21), Eustis (35) and Wheeler (36), and a case in an army officer reported by Nichols (37). Nichols states that when his case was reported everyone said that this was an instance of pellagra in which the food factor could be ruled out, presumably, because there could be no question of the patient not having had a good diet available, but on going into the history of the case with the patient's sister he found that the patient "had always been a crank on diet, had never eaten meat, and always carried crackers around in his pockets."

If the dietary theory is sound and a difference in diet between pellagrin and non-pellagrin is demonstrable then, it has been suggested, a difference between the diet of a community or locality in which only



exceptional, if any, cases occur and that of one in which the disease is highly prevalent should also be demonstrable. This is a reasonable expectation. Unfortunately, however, the attempt to demonstrate a difference in such circumstances calls for a laborious inquiry not only as to the diet directly but also as to the climatic, economic and other possible conditions that might affect the character of the food supply of a community or locality and thus, indirectly, of the character of the diet of its people. The observers who have reported that a significant difference is not demonstrable (7) (8) (9) (65) have reached this conclusion, we believe, because of inadequate and faulty methods of study of a difficult problem. The more soundly oriented inquiry carried out by Vedder (17) and that by the workers of the United States Public Health Service (6) resulted in adducing evidence that justified at least a strong presumption of the existence of a difference in household diet of contrasting communities. Thus, making due allowance for certain inherent difficulties, indications of a difference in diet as between pellagrin and non-pellagrin whether regarded as individuals, households or communities are frequently demonstrable or may reasonably be inferred.

In this connection the question naturally arises whether the marked annual fluctuations in pellagra prevalence, sometimes observed, can also be associated with fluctuations in diet. It has indeed been argued (67) that it is difficult to believe that the people of any considerable area should make such radical changes in their diet as would explain these fluctuations in prevalence. That this is a hasty and superficial view will at once be realized when it is recalled that quite similar fluctuations in prevalence are characteristic of such dietary diseases as scurvy, and beriberi, so that obviously considerable populations may make or, rather, may be obliged by circumstances to make "radical" changes in their diet. In reality, however, there is no need to assume that the changes in diet must be of a "radical" character. It seems to us quite possible that relatively slight and, superficially, perhaps quite inappreciable quantitative shifts may suffice to change what was perhaps a just sufficient diet into one more or less deficient in some one or more respects. Recalling the intimate relation that exists between economic conditions and pellagra incidence and recalling further that economic conditions are at times subject to violent

fluctuations, one can readily perceive the nature of the force that may oblige the people of a household, of a community or even of a nation to modify their diet for worse or, it may be, for better. The depression in the price of cotton in 1914 consequent upon the outbreak of the war in Europe was followed by a great increase in pellagra in the cotton growing area of the United States in 1915. The recovery in the price of this staple during 1915 was followed by an equally or even more notable reduction of the disease in 1916. Can it be believed that the sharp restriction of credit that the planter or the merchant in the plantation area of the Southern States was obliged to impose on the plantation labor in the fall and winter of 1914 in consequence of his inability to sell his crop without loss was without effect on the diet of those people? No one acquainted with the agricultural economic organization obtaining in the plantation area will have any doubt of the answer.

There is much reason to believe, therefore, that the year to year fluctuations in pellagra prevalence are associated with fluctuations in diet and that these are reflections of fluctuations in economic conditions.

Passing now to the question of the place of diet in the treatment of pellagra, we find that opinion has varied considerably in the course of the long history of the disease but it is worthy of note that over half a century ago Roussel (3), on the basis of his own observations and the experience of others, assigned to diet the place of first importance.

The testimony of many careful observers and the results of recent studies all go to show that in uncomplicated cases of average severity the administration of a diet containing a generous allowance of milk and fresh meat is quite regularly followed by clinical improvement. With only rare exceptions, provided the patient cooperates fully in taking the diet, this improvement continues progressively to eventual complete clinical recovery without the use of any medication except such as may be needed to mitigate distressing symptoms or complications. Should the cooperation be unsatisfactory or the diet for any reason be inadequate, the attack takes a very different course. In the milder attacks the manifestations, particularly the eruption, may clear up and the attack may seem to subside. But such seeming improvement is temporary. After a variable period (possibly of weeks) the

manifestations reappear perhaps again to subside but sooner or later these remissions cease. In other, as a rule more marked, cases no remissions occur, the attack with or without a period of seemingly stationary symptoms becoming progressively more pronounced and severe. Even at such more advanced stage a favorable change in food intake may be followed by improvement and recovery. It would seem clearly indicated therefore that diet operates as a dominating factor in controlling the clinical course and outcome of the attack. A conclusion that is strengthened by the fact that there are no observations however discordant they may have been thought to be that are really inconsistent with it (38).

That the specific treatment of pellagra resides in diet is further and more convincingly shown by the fact that the clinical recovery obtained by proper feeding is maintained as long as a proper diet is continued. In other words, recurrence of the disease so long dreaded by both laity and physician does not take place in those adequately nourished. This was for the first time demonstrated by studies carried out some ten years ago by Goldberger, Waring and Willets (39), and has since been confirmed by other workers (40) (41).

Not only was it demonstrated in those studies that the disease does not recur in those previously attacked but, still more, that it does not occur at all in those subsisting on an adequate diet. Since care was taken to make no changes in sanitary and hygienic conditions, nor as regards the character of new admissions to the institutions in which those studies were made, the complete prevention of both recurrent and new cases proved conclusively that pellagra may be prevented by diet without the aid of any other factor, hygienic or sanitary. And, it may be added, there is no good evidence that the disease can be prevented by any other means.

Not only has it been demonstrated that the disease is completely preventable by diet but, what is more, the production of the disease by diet has also been shown to be possible. In 1915, Goldberger and Wheeler (16) carried out an experiment at one of the Mississippi penitentiaries in which by feeding a diet resembling such as in previous observations they had found associated with a high incidence of the disease they succeeded in producing the disease in definitely recognizable form in at least six of eleven volunteers, all white male con-

victs As controls they had the other residents of the penitentiary, 120 in all, of whom 47 were under observation throughout the experimental period None of the controls developed any recognizable evidence of the disease

This experiment has not escaped criticism Shortly after the appearance of a preliminary report, MacNeal (42) (43) questioned its validity by casting doubts on the diagnosis of the experimental cases MacNeal's criticism has recently been echoed by Merk (66) of Innsbruck Referring to MacNeal's criticism, Wilson (44) of the School of Medicine of Cairo, Egypt, says "MacNeal casts doubts on the correctness of the diagnosis, no one, however, with some experience of the disease can fail to be convinced, after reading Goldberger's recent paper, that these men suffered from pellagra, the writer from recent experience in Egypt would be inclined to believe, from the peculiar lingual and intestinal symptoms described, that four others might well have been included as pellagrous, leaving one only out of the eleven who does not appear to have become affected" If it be permissible to amend Professor Wilson's comment we would suggest that to be convinced that these men had pellagra, one other requirement must be fulfilled—namely, the possession of an open mind

Although relatively great progress has in the past ten years been made in our knowledge of pellagra, this progress has been slow when compared with that recently recorded in connection with certain other diseases of nutrition The difference is largely if not altogether due to the fact that for pellagra an experimental animal has been lacking There is reason to believe, however, that this deficiency has now been supplied

In August, 1917 Chittenden and Underhill (45) reported the experimental production in dogs, by feeding, of a pathological condition which they regarded as closely resembling human pellagra Wheeler, Goldberger and Blackstock (46) have identified this experimental condition with the spontaneously occurring disease of dogs known to American veterinarians as black tongue It is of interest to note that the resemblance of the spontaneous disease to human pellagra had been commented on by at least one observer (47) even before Chittenden and Underhill's publication More recently Underhill and Mendel (48) have briefly reported some results of a study of this con-

dition begun in 1918 and not yet completed. They state that the syndrome in the dog is associated with a lack of some unknown constituent of butter fat which is different from fat soluble A since cod liver oil does not protect. They have reached the conclusion also that fresh beef possesses some protective action but in the absence of a sufficiency of the unknown effective agent present in butter the disease may be induced on a diet containing much meat but a longer period of time is necessary. The same statements are reported as applicable to casein which has been purified by boiling with alcohol. They have found also that egg yolk confers a certain degree of protection but is not as effective as butter fat. Carrots are reported as particularly effective in alleviating the syndrome when it is once initiated. In a paper that has just appeared Goldberger, Wheeler, Lillie and Rogers (49) report in a preliminary way, some results of a study of experimental black tongue that suggest very strongly that this condition and human pellagra are etiologically identical. They have induced this canine disease by feeding dogs certain diets previously found associated with the occurrence of pellagra, including the diet used in the human experiment carried out at a Mississippi penitentiary. Based on their experience with pellagra they have constructed a diet with which they are able regularly to induce this disease in the dog in from one to three or four months. They report that substances such as yeast, yeast extract and fresh lean beef, that were found to possess black tongue-preventive potency, have when tried in pellagra been found efficient preventives of the human disease and, conversely, that the substances such as butter fat, cod liver oil and casein that had failed in pellagra or that, like milk, were of low pellagra-preventive potency, when tried in black tongue failed or were feeble as preventives of the canine disease. In consequence of these striking findings they have adopted the working hypothesis that black tongue of dogs is the analogue of pellagra in man.

In the same publication these workers also report results that seem to indicate that the rat too will probably be found to serve as an experimental animal in the study of pellagra and of black tongue. We shall return to this presently in another connection.

Thus it would seem that we are warranted in concluding not only that indications of a difference in diet between pellagrin and non-

pellagrin are demonstrable and that the disease is curable and completely preventable by a proper diet but also that it may be experimentally produced by diet in man and with a high degree of probability (its analogue) in the dog, and possibly the rat, thus proving that the implications of the dietary hypothesis, so far as they have been tested, are true. Accordingly, in the light of the indications afforded by the evidence previously considered it may be concluded that diet is the primary controlling factor in the causation of the disease.

Accepting this conclusion the question now arises as to the nature of the essential dietary fault upon which the production of the disease depends. Needless to say, many suggestions along this line are to be found in the voluminous literature. The older of these, such as that of quantitative inadequacy, of monotony of diet, of monophagism, of spoilage or, specifically, of spoiled maize, and of carbo-hydrate excess have all been shown to be untenable. We may therefore pass on to a consideration of those more recently advanced. But even of these only the most immediately pertinent can for obvious reasons be considered.

We shall begin with the views advanced by Funk (50). In 1912 this worker provisionally included pellagra in a group of "deficiency diseases," all of which, he stated, could be prevented and cured by the addition to the diet of certain preventive substances called by him "vitamines."

Interesting and stimulating as this generalization has proved to be he advanced in its support, so far as pellagra is concerned, only certain epidemiological and clinical analogies to beriberi. More recently (51) he has expressed himself as inclined to the view—which he not altogether correctly credits to Goldberger—that the following factors are possible: "Partial lack of vitamins, lack of animal protein, lack of a still unknown vitamine, the combined influence of all these factors."

Inspired by Funk's and the other then recent developments in beriberi, Sandwith (52) in 1913 suggested that pellagra might be a "deficiency disease waiting for a vitamin to be discovered."

As the result of extensive studies, Voegtlin (53) in 1914 expressed the opinion that in the study of the etiology of pellagra serious con-

sideration would have to be given to a deficiency or absence of certain vitamins in the diet, to the toxic effect of some substances, as aluminum, which occur in certain vegetable food and to a deficiency of the diet in certain amino acids. Later, from a study of the influence of vitamins on the clinical course of pellagra, Voegtlin (54) in association with Neil and Hunter reported that the administration of extracts from yeast and rice polishings which were highly efficient for the prevention of avian polyneuritis, in general failed to modify the course of the disease, but the administration to pellagrins of protein-free extracts obtained from liver and thymus gland, presumed to contain both the antineuritic substance and the fat soluble vitamin, "was followed by improvement in their condition apparently comparable to that produced by the consumption of a diet rich in fresh animal proteins." They concluded that "the dietary defect responsible for pellagra is distinctly (qualitatively) different from and perhaps more complex than the one causing fowl polyneuritis and human beriberi."

In 1918 McCollum, Simmonds and Parsons (55) on the basis of results of studies in rats, expressed the belief that pellagra is primarily associated with the unsatisfactory character of three dietary factors, namely, fat-soluble A, mineral elements and protein mixture. A year later, after having attempted to produce in rats a condition analogous to pellagra in man by feeding with diets similar to the diet employed by Goldberger and Wheeler in their experiment in convicts, and having observed in them only a "generalized poor condition," they (56) concluded that pellagra is caused by an infectious agent. More recently McCollum (57) has stated that "it seems established that pellagra is in some manner caused by faulty diet," but expresses no opinion as to the nature of the fault.

As the result of studies of diets of various groups, pellagrous and non-pellagrous, carried on in Egypt Wilson (44) reported in 1921 that the etiological factor is a deficiency of protein in the food best determined by an estimation of its biological value by means of Thomas' figures.

In 1920 Wood from some experiments with fowls, and by reason of seemingly favorable results of treatment with maize germ and wheat bran, reported that he was disposed to suspect that a vitamin-B

deficiency is involved in pellagra but pointed out, at the same time, that there may be something else in the maize germ and the cortex of wheat that may account for the results observed

Beginning their investigation of pellagra in 1914, Goldberger and associates have reported a series of studies the results of which they have interpreted as permitting the exclusion of one after the other of the known dietary essentials—until in 1922 they (58) concluded, on the assumption that all the dietary factors essential in human nutrition were known, that the essential etiological dietary factor is a specific defect in the amino-acid supply, probably in the nature of a deficiency of a special combination or combinations of amino acids. Realizing, however, that the assumption that all dietary essentials were known was of doubtful validity (59) but considering that as between the protein and an as yet unrecognized factor the probabilities favored the former as being the one concerned, they undertook a study of the therapeutic and preventive value of the protein of casein late in the summer of 1922. Early in 1925 they (60) reported that while the casein had had a beneficial effect on the general nutrition of their patients and in considerable measure prevented or, at least, notably delayed the development of the distinctive eruption, it did not prevent, though it may have delayed the relapse or recurrence of some of the other symptoms of the disease. They concluded therefore that the protein factor, if it be concerned in pellagra is not the sole preventive or causative factor and thus that some other heretofore unrecognized or unappreciated dietary complex also plays an essential rôle. This interpretation was supported by the results of a preventive study of dried skim milk when contrasted with those of a study of fresh buttermilk, on the basis of protein content dried skim milk proved itself distinctly inferior to fresh buttermilk. It was supported still more, perhaps, by the results of a study of the pellagra-preventive potency of dried yeast. In a daily dose of between 15 and 30 grams, representing less than 15 grams of protein, dried yeast was found very efficient in preventing the disease, a result that in view of the proved inadequacy of casein it was difficult or impossible to credit to its protein alone. They thought too that in view of the relatively small amount of protein furnished by the effective dose of yeast the special pellagra-preventive factor, which they designated as factor P-P,



would seem capable of preventing the disease with little if any co-operation from the protein and, further, that it is possible that factor P-P plays the sole essential rôle in the prevention and causation of the disease

This interpretation is strengthened by the results of further studies just reported by these workers (49) In tests of fresh lean beef and a commercial dried water extract of yeast they found both efficient pellagra-preventives In this study the daily allowance of beef was 200 grams (7 ounces) and of the yeast extract 15 grams In view of their previous experience with casein the protein of which in a daily allowance of 60 grams had been found not fully adequate entirely to prevent the disease, it is reasoned that since the allowance of beef yielded but about 45 grams of protein and that of the yeast extract could not have contributed over an equivalent of about 7.5 grams of protein, the potency of the beef and that of the yeast extract could not well be attributed to their protein alone They therefore concluded that lean beef and yeast extract contain factor P-P and that this factor, in view of the effectiveness of the yeast extract with its small yield of protein, probably plays the primary rôle in the prevention and causation of pellagra

They point out that the demonstration of the pellagra-preventive potency of yeast and yeast extract which, aside from protein and a negligible trace of vitamin A, has heretofore been believed to contain only the water soluble B vitamin naturally raises the question of the relation of factor P-P to vitamin B They recall that although "water soluble B" has quite generally been considered as representing a single dietary factor with both antineuritic and growth-promoting properties (61), a number of investigators (62) have not accepted this view, inclining to the belief that it includes at least two distinct dietary essentials, namely, the antineuritic or beriberi vitamin to which alone, following Funk, the designation "vitamin B" belongs and a "growth-promoting" factor which some workers have attempted to identify with bios (63).

That vitamin B in the sense of the beriberi vitamin or antineuritic is not concerned in the etiology of pellagra or, in other words, that it is distinct from factor P-P and that these two factors may perform their physiological functions one independently of the other is, they

state, even aside from any other evidence, quite conclusively shown by the rarity of association of beriberi and pellagra. The fact that these diseases in rare instances do occur together in the same patient in their judgment only emphasizes the significance of the rarity of such cases. Thus although the diet may be deficient in both the beriberi and pellagra-preventive essentials, ordinarily in relation to these diseases it is deficient in one and not, or clinically but inappreciably, in the other factor.

With respect to the relation of factor P-P to the so-called growth-promoting essential, heretofore possibly included in the term "water soluble B," Goldberger and associates bring forward evidence which seems strongly to point to their probable identity.

They state that having found yeast to contain the factor concerned in the prevention of black tongue and of pellagra, and having assumed, for reasons already referred to in a preceding connection, that this factor is the same for both conditions, they undertook a study of the characters of this factor as it exists in yeast. By means of black tongue-preventive tests in the dog they found that factor P-P is adsorbed from an acidulated water extract of yeast by English fullers' earth (Seidell's activated solid), that it is destroyed by charring the yeast but is damaged but little, if at all, when the yeast is heated in the steam autoclave at fifteen pounds pressure for 2½ hours. They report further that when young rats are fed a diet that is complete for growth except as to "water soluble B" and contains as the sole source of this vitamin as much as 30 or 40 per cent of such autoclaved yeast (Chart 1, Chart 2, period 4), their growth is quickly arrested, then their weight declines and they die with or without symptoms of polyneuritis, although the same yeast before autoclaving when forming 8 or 10 per cent of the diet furnishes sufficient "water soluble B" for good though not optimal growth. Thus, they point out, according to current ideas the autoclaving does not notably affect factor P-P but (in yeast) inactivates the "water soluble B." Evidently, too, factor P-P is not of itself growth-promoting in the rat. Furthermore, if the so-called growth-promoting water soluble vitamin of the yeast is distinct from both the antineuritic and the P-P factor, then clearly either the heating has inactivated it or like factor P-P it is not a special growth factor.

But that P-P or some associated, and in yeast relatively heat resisting, factor is essential for the growth of the rat is strongly indicated by the results of some work with autoclaved yeast recently reported from the Hygienic Laboratory by Smith (64) and clearly shown by Goldberger and associates by the following

1 Young rats were fed a diet complete for growth except as to "water soluble B" and containing as the sole source of "water soluble B" as much as 30 or 40 per cent of autoclaved yeast which from tests in dogs had been shown to contain factor P-P, the rats quickly declined in weight, after a slight initial rise, and died with or without

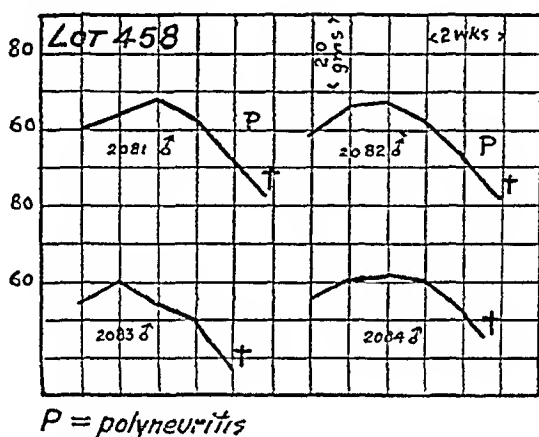


CHART 1 Weight curves of four young albino rats (Lot 458) whose diet (No 227) included as the sole source of "water soluble B" 27 per cent of autoclaved yeast. Slight initial growth was followed by arrest and continued loss of weight terminating in death. Two of the animals developed signs of polyneuritis. (After Goldberger, Wheeler, Lille and Rogers.)

signs of polyneuritis, thus giving proof of an antineuritic deficiency (Chart 1, Chart 2, period 4)

2 Young rats were fed a diet complete for growth except as to the "water soluble B" but containing as the sole source of this vitamin as much as 40 per cent of a preparation of an alcoholic extract of corn meal (Chart 2, period 1) that was found potent in alleviating or curing polyneuritis in the rat. The animals notwithstanding an abundance of antineuritic quickly declined in weight after slight initial growth.

3 When, however, young rats were fed a diet as before complete for growth except as to "water soluble B" but containing as sources

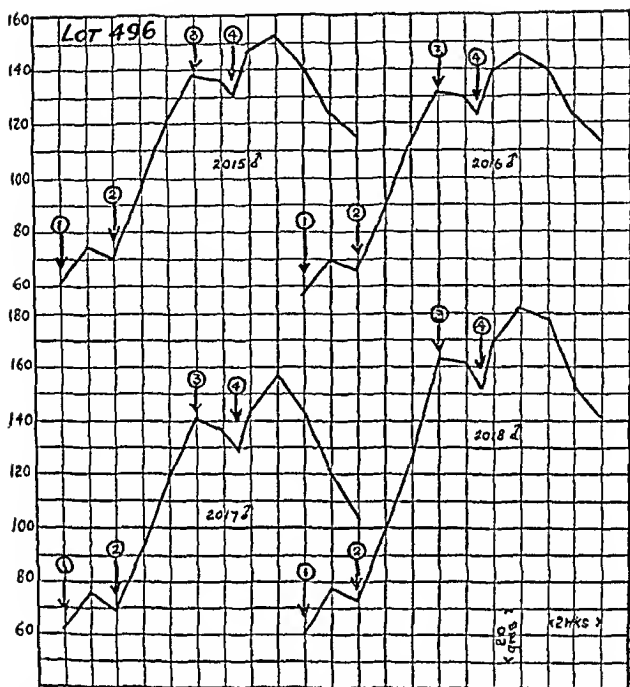


CHART 2 Weight curves of four young albino rats (Lot 496) during four dietary periods. During period 1 their diet (No. 218) included as the sole source of "water soluble B" 40 per cent of an alcoholic extract of corn. After an initial gain in weight they began to lose, whereupon there was added to their diet 9 per cent of yeast previously autoclaved at 15 pounds for 2½ hours. This was at once followed (period 2) with a resumption of growth which was well maintained during three weeks at the end of which a change in diet was again made. This change consisted of the withdrawal of corn extract and autoclaved yeast thus giving them the basic diet (No. 206) without any known source of "water soluble B". Growth was at once arrested followed by a downward trend in weight (period 3). Now another change in diet was made. The basic diet (No. 206) was replaced by one which included 40 per cent of autoclaved yeast as the sole source of "water soluble B" (diet No. 239). This change was followed by a resumption of growth which lasted but a short time and was followed by a progressive loss in weight. Thus neither 40 per cent of the corn extract nor 40 per cent of the autoclaved yeast when the sole source of "water soluble B" permitted the rats to grow but when only 9 per cent of the autoclaved yeast was added to the diet containing the corn extract growth took place and was maintained. (After Goldberger, Wheeler, Lillie and Rogers.)

of this vitamin as little as 8 or 10 per cent of the autoclaved yeast and as little as 5 per cent of the preparation of the extract of corn meal, the animals grew (Chart 3, Chart 2, period 2, Chart 4)

Again, when young rats were fed a diet complete for growth except as to the "water soluble B" and containing as the sole source of this vitamin 20 per cent of dried fresh lean beef which, judging by ex-

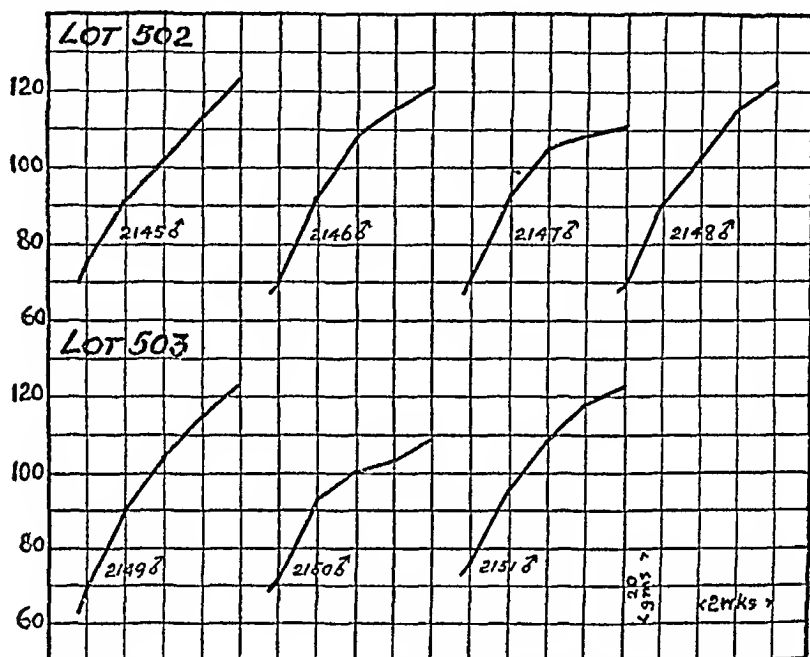


CHART 3 Weight curves of two lots of young albino rats The diet of both was free of "water soluble B" except as supplied by 5 per cent of a corn extract combined with, in the case of lot 502, 8 per cent (diet 243E) and in the case of lot 503, 10 per cent (diet 243F) of autoclaved yeast Although neither preparation alone when the sole source of "water soluble B" even to the extent of 40 per cent of the diet permits growth when, as here, much smaller proportions of each are combined growth takes place thus proving conclusively that this is not simply an additive phenomenon The growth of these animals is at a somewhat reduced rate, for optimal growth the percentages of both corn extract and autoclaved yeast would have to be increased (After Goldberger, Wheeler, Lillie and Rogers)

perience in both black tongue and pellagra, contains factor P-P, such animals after slight initial growth declined in weight and died with or without polyneuritis, thus indicating an antineuritic deficiency (Chart 5, period 1) When, however, on the appearance of signs of polyneuritis there was included in the diet of these animals as little as 5

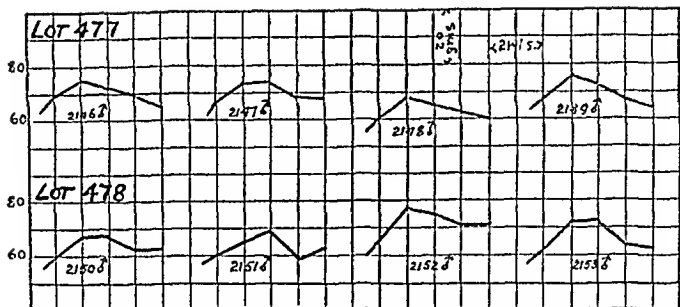


CHART 4 Weight curves of two lots of young albino rats The diet of both was free of "water soluble B" except as supplied by 6 per cent (Lot 477, diet 238B) and 12 per cent (Lot 478, diet 238C) respectively of a corn extract Growth was quickly arrested (After Goldberger, Wheeler, Illie and Rogers)

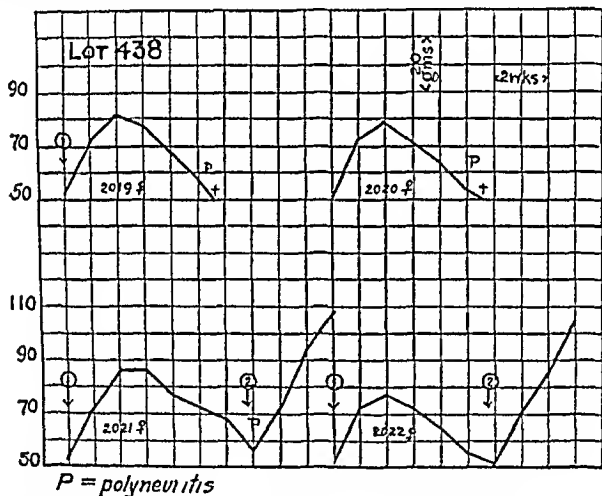


CHART 5 Growth curves of young albino rats (Lot 438) whose diet during period 1 included as the sole source of "water soluble B" 20 per cent of dried fresh beef After some initial growth there was arrest followed by loss of weight with the development of signs of polyneuritis in three of the animals After two of these died the diet was modified by adding 5 per cent of our corn extract (diet 219A) This was followed by disappearance of the signs of polyneuritis in the survivor showing these, with prompt resumption of growth in both survivors (period 2) The beef contained sufficient P P but was deficient in antineuritic The small addition of corn extract supplied enough of this to supplement P P sufficiently to permit growth to take place (After Goldberger, Wheeler, Illie and Rogers.)

per cent of the preparation of alcoholic extract of corn, 40 per cent of which as the sole source of "water soluble B" in a diet does not enable the rat to grow, the animals that were not too far gone recovered from polyneuritis and resumed growth (Chart 5, period 2). Clearly the alcoholic extract of corn although capable of curing polyneuritis in the rat does not of itself promote growth but does permit or promotes growth when combined with a suitable proportion of a P-P containing substance, such as autoclaved yeast or beef, which itself, within certain limits at least, neither prevents polyneuritis nor permits growth

Thus autoclaved yeast and beef muscle were shown to contain a factor distinct from the polyneuritis-preventing essential which, in combination with the antineuritic, is necessary for the growth of the rat. This factor which is perhaps identical with the yeast growth-stimulant or bios is at present indistinguishable from factor P-P, but whether the two are really the same, as seems very probable, will require further study to determine.

Summing up, it may be stated that the available evidence seems to leave no reasonable doubt but that pellagra is caused by a faulty diet. The primary dietary fault appears to be of the nature of a deficiency of a factor P-P, very probably but not certainly identical with a dietary essential, heretofore included with the antineuritic under the designation "vitamin B", which some workers have attempted to identify with bios.

#### REFERENCES

- (1) *Memorias de Historia Natural y Medica de Asturias por el Doctor Don Gaspar Casal* Reimpresas y Anotadas por A. Buylla y Alegre y R. Sarandeses y Alvarez Oviedo, 1900
- (2) ROSSI *Am Jour Insanity*, 1913, lxi, 941
- (3) ROUSSEL *Traite de la Pellagra*, etc Paris, 1866
- (4) LOMBROSO *Die Lehre von der Pellagra* Berlin, 1898
- (5) SAMBON *Progress Report on the Investigation of Pellagra* Reprint Jour Trop Med & Hyg London, 1910
- (6) GOLDBERGER, Wheeler and Sydenstricker *Public Health Reports*, Washington, D C, 1920, xxxv, 2673-2714
- (7) Siler, Garrison and MacNeal *Arch Int Med*, 1914, xiv, 453-474
- (8) Jobling and Petersen *Jour Infect Dis*, 1916, xviii, 501
- (9) JOBLING AND PETERSEN *Jour Infect Dis*, 1917, xxi, 109-131
- (10) GOLDBERGER, Wheeler and Sydenstricker *Public Health Reports*, Washington, D C, 1920, xxv, 1701-1714  
Also unpublished data

- (11) SILER, GARRISON, AND MACNEAL Arch Int Med, 1917, xiv, 683
- (12) GOLDBERGER, WHEELER AND SYDENSTRICKER Unpublished data
- (13) NESBITT J Am Med Assn, 1916, lxi, 647
- (14) RICE Southern Med J, 1916, lx, 778-785
- (15) SILER, GARRISON AND MACNEAL Arch Int Med, 1917, xx, 198
- (16) GOLDBERGER AND WHEELER Bull 120, Hygienic Laboratory, Public Health Service, Washington, D C, 1920
- (17) VEDDER Arch Int Med, 1916, xvi, 137
- (18) BALZ AND MIURA Berberi oder Kalke, etc Mense's Handbuch der Tropenkrank, 1905, ii, 140-174
- (19) SCHEUDF Berberi, Diseases of Warm Countries London, 1903 187-226
- (20) KIMBALL Am J Pub Health, 1923, xiii, 81-87
- (21) ROBERTS J Am Med Assn, 1920, lxxv, 21-25
- (22) TANNER AND ECHOLS J Am Med Assn, 1921, lxxvi, 1337-1338
- (23) DEARMA Southern Med Jour, 1914, vii, 515-525
- (24) HARRIS J Am Med Assn, 1913, lx, 1949-1950
- (25) FUNY Die Vitamine, Wiesbaden, 1914
- (26) BASS International Conference on Health Problems in Tropical America Boston, 1924 720
- (27) LAVENDER AND FRANCIS J Am Med Assn, 1914, lxiii, 1093-1094  
FRANCIS Bull 106, Hygienic Laboratory, Public Health Service, Washington, D C, 1917
- (28) BUNTA, DE ROLANDIS cited by Roussel (3)  
McCAFFERTY Gulf States J Med and Surg and Mobile Med and Surg J, 1909 228-236  
GOLDBERGER Public Health Reports, Washington, D C, 1916, xxxi, 3159-3173
- (29) KULZ Arch f Schiffs- u Trop Hyg, 1918, xxi, 401-431
- (30) HARRIS N Orl Med & Surg, J, 1919-20, lxxii, 452-467
- (31) GOLDBERGER Public Health Reports, Washington, D C, 1914, xxix, 1683-86
- (32) ENRIGHT Lancet, 1920, (1) 998-1003
- (33) GOLDBERGER, WHEELER AND SYDENSTRICKER Public Health Reports, Washington, D C, 1920, xxxv, 648-713
- (34) LUSTIS J Am Med Assn, 1920, lxxv, 26
- (35) WHEELER Public Health Reports, Washington, D C, 1920, xxxv, 2509-2514  
Idem, 1924, xxxix, 2197-2199
- (36) NICHOLS International Conf On Health Problems in Trop America Boston, 1924 721
- (37) GOLDBERGER J Am Assn, 1922, lxxvii, 1676-1680
- (38) GOLDBERGER, WARRING AND WILLETS Pub Health Reports, Washington, D C, 1915, xxx, 2117-3131  
GOLDBERGER, WARRING AND TANNER Pub Health Reports, Washington, D C, 1923, xxxvii, 2361-2368
- (39) WHITE Report on an Outbreak of Pellagra Amongst Armenian Refugees at Port Said, 1916-17 Cairo, Egypt, 1919
- (40) STANLEY Trans Roy Soc Trop Med. & Hyg, 1920 16
- (41) MACNEAL J Am Med Assn, 1916, lxi, 975-977
- (42) MACNEAL Am J Med Sc, 1921, clxi, 469
- (43) WILSON Jour Hygiene, 1921, xx, 1-59



- (45) CHITTENDEN UND UNDERHILL *Am J Physiol* , 1917, *cliv*, 13
- (46) WHEELER, GOLDBERGER AND BLACKSTOCK *Pub Health Reports*, Washington, D C , 1922, *xxvii*, 1063-1069
- (47) SPENCER *Am J Veterin Med* , Chicago, 1916, *xi*, 325
- (48) UNDERHILL AND MENDEL *Pub Health Reports*, Washington, D C , 1925, *xl*, 1087-1089
- (49) GOLDBERGER, WHEELER, LILLIE AND ROGERS *Pub Health Reports*, Washington, D C , 1926, *xl*, 297-318
- (50) FUNK *J State Med* , London, 1912, *xx*, 341-368
- (51) FUNK *The Vitamines*, Baltimore, 1922
- (52) SANDWITH *Trans Soc Trop Med and Hyg* , 1913, *vi*, 143-148
- (53) VOEGTLIN *J Am Med Assn* , 1914, *lxiii*, 1094-1096
- (54) VOEGTLIN, NEILL AND HUNTER *Bull 116*, Hygienic Laboratory, Public Health Service, Washington, D C , 1920
- (55) MCCOLLUM, SIMMONDS AND PARSONS *J Biol Chem* , 1918, *xxxiii*, 421
- (56) ————— *Idem*, 1919, *xxxviii*, 125
- (57) MCCOLLUM *The Newer Knowledge of Nutrition* New York, 1925
- (58) GOLDBERGER AND TANNER *Pub Health Reports*, Washington, D C , 1922, *xxxvii*, 462-486
- (59) GOLDBERGER AND TANNER *Pub Health Reporays*, Washington, D C , 1924, *xxxix*, 87-107
- (60) GOLDBERGER AND TANNER *Pub Health Reports*, Washington, D C , 1925, *xl*, 54-80
- (61) SHERMAN AND SMITH *The Vitamines* New York, 1922
- (62) MITCHELL *J Biol Chem* , 1919, *xl*, 399  
EMMETT AND LUROS *J Biol Chem* , 1920, *xlvi*, 265
- (63) EMMETT AND STOCKHOLM *J Biol Chem* , 1920, *clvii*, 287  
SOUZA AND MCCOLLUM *J Biol Chem* , 1920, *xliv*, 113  
FUNK AND DUBIN *J Biol Chem* , 1921, *xlvi*, 437  
HEATON *Biochem J* , 1922, *xvi*, 800
- (64) SMITH *Pub Health Reports*, Washington, D C , 1926, *xl*, 201-207
- (65) SILER, GARRISON AND MACNEAL *Arch Int Med* , 1914, *xiv*, 292-373
- (66) MERK *Zentralbl f Haut u Geschlechtskrank* , 1925, *xvii*, 241-411
- (67) JOBLING AND ARNOLD *J Am Med Assn* , 1923, *lxxx*, 365-368

## CONSTITUTION AND TYPE IN RELATION TO DISEASE<sup>1</sup>

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From almost the beginning of medical history the rôle of constitution in relation to disease has been recognized, yet in spite of the age of this problem very little accurate scientific knowledge is available bearing on an exact connection between a definite constitution and the nature of its diseases.

Ultimately no doubt this problem must require much statistical and biometrical control but in its present phase considerable general morphological data are much needed. It is certainly equally as important to ascertain what to measure as it is to make the measurements. Undoubtedly much time and effort have been fruitlessly spent in making many careful measurements of meaningless characters. One is certainly highly optimistic who can survey the enormous accumulation of anthropometric figures and indices without feeling a considerable degree of disappointment over the almost complete absence of explanation or analysis of the causal elements in racial differentiation. The simple and very significant differences in cephalic index have scarcely given the slightest clue to the cause of head shapes or to racial relationships. The quite distinct anthropological differences between the two well recognized human types have indicated practically nothing as to their real nature or origin. Many anthropologists have considered head shape a most important racial feature yet if one should use such a criterion in classifying the various breeds of dogs he would become considerably confused. The dolichocephalic head of the Esquimo and the brachycephalic head of an achondroplastic man should cause some uncertainty regarding the use of head index as a racial criterion. This is not to be taken as a criticism of the anthro-

<sup>1</sup> DeLamar lecture delivered before the School of Hygiene and Public Health, Johns Hopkins University, March 15, 1926.

pometric method in itself, but the way in which it has been employed has not proved very instructive

During the past few years there has been a decided revival of interest in the study of the relation between constitution and predisposition to disease. However, in presenting the subject I have thought it best not to attempt a discussion of the specific problems on which we are at present engaged, and from which only very partial and somewhat indefinite results are available but, rather, to devote the present consideration to the general problem of constitution and the methods by which this problem may be definitely approached and possibly analyzed.

In the first place, before we are able to understand the relation of constitution and type to disease, it would seem necessary to know exactly what "type" and what "constitution" actually mean. As I consider the terms, type and constitution are not synonymous. The type indicates the fundamental character of the individual and remains fixed throughout life, while the constitution of the same individual changes during different life periods and may readily be greatly modified at any time. For example, a linear type individual may during adult life develop mild acromegalia—this does not alter the type though the constitution of the person becomes greatly modified. If pure types do exist, naturally type hybrids also occur. What are their characteristics and how are they to be recognized and classified? Probably a great deal of the uncertainty surrounding the connection between constitution and disease results from the fact that there is no clean cut agreement as to what the different constitutions actually represent. From the medical standpoint scarcely anyone has sought to determine the basis or origin of a definite type or constitution. There must be some uniform criteria for contrasting the several kinds of constitutions, and before this is clearly determined it is difficult to proceed. An accurate study of constitution itself seems to me the problem of first importance.

The general study of the whole subject has, however, largely proceeded the other way around. Physicians interested in disease have more or less intuitively come to believe that certain types of people do exist and seem predisposed to particular kinds of diseases. There is often a pronounced diathesis on the part of a given patient towards

particular diseases There is, for example, the tubercular tendency Many discerning physicians are more or less successful in recognizing these tubercular disease types But when the uninitiated seeks a description of the particular type it is most difficult, if not impossible, to obtain it except in vague, general and indefinite terms, and in almost no cases has serious study been devoted to the very important question of the nature, origin or development of the given type or to the very fundamental question,—whether an actual type is really concerned

What is there peculiar about the composition or constitution of the particular patient which causes him to be subject to tubercular disease in contrast with the more resistant individual? Is this difference genetic or developmental in origin, or both, or is it due to differing degrees of an acquired reaction on the part of persons who have been subjected to some definite and peculiar environmental stress or condition? The answers to such questions as these are certainly necessary for a better understanding of the problem

The physician studying constitution frequently confines his attention to only one life period of the individuals involved, and usually to the most static period, the adult Dr Draper in his recent anthropometric study of certain disease groups has confined his material to persons between the ages of eighteen and sixty Such restriction eliminates almost all growing and developing individuals as well as many of the important late senility conditions A study of such groups leads one to overlook arrested and childlike tendencies in particular persons as well as many abnormal secondary growth reactions The rare occurrence of a typically adult disease among children may furnish a simpler clue to the constitutional diathesis than the study of great numbers of adults with this disease Deviations and odd conditions often give the plan away more decidedly than routine happenings

Constitution itself is not a static or fixed affair but is a developmental condition depending upon the genetic composition of the individual to a large extent, but also depending in a most important degree on the manner of development and growth The constitution of a given individual is actually a different thing at different life periods In this way constitution is to be differentiated from type

which, as a rule, is characteristic and true for the individual throughout life—type is, as it were, the static element which underlies the changing constitution

The prenatal period is probably the most important in determining all later constitutional conditions since at this time the actual gross body form and structure is being laid down and any environmental peculiarity may exert a marked influence on the course of development and may actually determine whether the individual will develop in a normal well-ordered fashion or into a deformed, crippled and deranged specimen. Thus prenatal stage, although probably the most important and the one on which all subsequent life stages directly depend, has been largely neglected and is almost unknown to the majority of physicians. A clearer understanding of the relation of constitution to type and to disease may be actually obtainable through a consideration of the embryonic and foetal development which has produced a given individual.

The constitution of babyhood is quite different from that of childhood. The undifferentiated and undeveloped baby reacts differently to the various types of food and other stimuli from the way in which the child does. The constitution of the child becomes considerably revolutionized at the time of puberty and the general reaction at this time is not entirely predetermined but may be modified by various environmental conditions, and youth, after puberty, passes through a stage of growth and maturity which largely depends on the success of the puberty changes themselves. Much is to be appreciated regarding the controlling elements in constitution by a study of these important changes. The final adult constitution is therefore a somewhat uncertain accomplishment which has been affected and influenced by both internal and external factors that have acted on the organism from the early stages of development until the final adult condition has been reached. Through all these various age periods of the constitution there exist distinct type differences which separate one group of age constitution from another.

Certain races tend to show characteristic constitutions which may differentiate them from other races in various ways, but aside from the general tendency of a well marked race to exhibit a more or less uniform racial constitution, there are individuals among all races which

show widely divergent constitutions, differing entirely from the average pattern. Such individuals are either due to developmental deviations from the general pattern or to genetic modifications, and they are very important in analyzing the nature of the normal race pattern.

From the above, as indicating the general situation, it becomes evident that we must determine whether different types actually do exist and what are their natures and general characteristics, since on these type differences constitution largely depends. A ready way to proceed may be to review in a general manner the information obtained from a study of lower forms. If types exist among the human population, it is quite probable that similar types also occur among other mammalian forms, particularly the domesticated animals.

I have been led to believe during the past few years that certain domestic mammals, such as dogs, exhibit in a pronounced way, a great many of the so-called types which have been recognized among men. In these lower forms many such types have actually been selected and preserved for centuries in some cases, and now constitute rather typical breeds or races of animals. The structural, physiological and psychological characteristics of a given breed are quite definitely maintained. By attempting to analyze these breeds through a comparison with certain experimental results, as well as with distorted developmental conditions, I believe we shall succeed in getting important information for a more logical understanding of the human conditions.

Before considering the types themselves we may briefly review the possible hereditary background of some exaggerated conditions in relation to certain disturbances and changes in the germ plasma. It has long been recognized that certain germ-cells in a normal parent may be weak and defective and it frequently happens among apparently good stock that peculiar genetic abnormalities arise. A very striking case in point has recently been presented by Sewall Wright from genetic studies on guinea pigs. A family of guinea pigs from ordinary stock began to produce a more or less definite abnormality affecting the development of the lower jaw and the position and development of the ears, a condition of otocephaly. The lines giving this peculiar condition were definitely recorded and all such animals could be traced

back to a single brother-sister mating. The descendants from mating, however, showed very different tendencies. Certain branches arising from the common ancestry failed entirely to show any abnormal development, while in other branches of the family a very high percentage of otocephalic individuals occurred in one generation and in another. Dr Wright found, on analysis, that this condition was transmitted as if multiple factors or a number of genetic unit genes were involved and the abnormality had probably arisen through some spontaneous modification in the genetic composition of the animals. The defect itself, however, is of the nature of a type of development arrest and without knowledge of the breeding record one would be inclined to interpret this situation as due to some developmental disturbance rather than to an heredity cause.

Modifications closely comparable to the above have been produced in experimentally treated animals. Certain chemical treatments when administered to guinea pigs and other animals seem to affect some of their germ-cells in a general way, causing these to give rise to poorly developed or actually abnormal individuals. The constitution and probably the type of these individuals are decidedly modified and differ from those of the general stock. An interesting result of this kind has recently been reported by Bagg and Little. Mice from a well known stock were subjected to short treatments by x-ray. In the first few generations of descendants from these treated animals were quite normal but during later generations very peculiar abnormalities appeared and, by selection, it was possible to secure animals which produced offspring everyone of which showed underdeveloped or abnormal eyes. Among the same group of animals an abnormal condition occurs, some individuals showing a complete absence of both kidneys while others may have abnormal kidneys or may have one normal kidney with the other entirely absent. A line of animals has been selected which breeds almost 100 per cent pure for kidney defects. Whether these peculiarities were actually induced by x-ray treatment or not is at present impossible to say since the experiment has not been successfully repeated, but for our present consideration this is unimportant. The fact of real interest is that a peculiar genetic composition has arisen in this race of mice which causes them to produce peculiarly defective specimens. The constitution of such

individuals is highly modified and they are certainly subject to definite structural diseases which are extremely rare among the stock population in general. A few other cases might be cited to show that the hereditary material itself may possibly become altered or modified so as to give origin to peculiar developmental processes which ultimately predispose the individual to very definite types of physical disease.

The nature of many of these defects which are definitely found to be germinal in origin is surprisingly similar to other defects which are induced by simply arresting the development of a typically normal embryo. In other words, the germinal modification seems to have caused simply a lowered developmental potential rather than to have altered any particular genetic character. When embryos are arrested at exact stages of development certain organs and parts are inhibited and modified in their structural development. It has been clearly demonstrated that these defects, which definitely modify type and constitution, are induced by disturbed development. The most convincing proof of this is shown by the frequent differences in developmental success attained by the two components of a double monster or united twin individuals. It commonly happens among joined or united twin individuals that one component is arrested or handicapped in its development while the other develops perfectly normally. In this case there can be no doubt that the abnormality of one individual is solely due to some developmental disturbance since the genetic basis of both components must necessarily be identical. These examples of general modification resulting from disturbed embryonic development are of course quite monstrous and exaggerated in their condition, yet I believe that milder expressions of many such conditions as these are most important elements in the general determination and development of the different kinds of individuals among the normal population. Various human types, as well as the types among lower animals, should be clearly recognized as definite growth reactions which result from slight distortion in either the internal or external factors which affect development. Among extreme cases it is often easy to demonstrate this fact and also to show something as to what the cause has been. Since as a rule an almost complete series of gradations exists from these extreme cases, up to the really normal individual, we are



finally justified in presuming that the slight deviations may be of the same general causal origin as are the more pronounced gross deformities

We may now examine some of the more usually recognized and accepted types and shall again start with rather extreme forms. All physicians recognize several classes of dwarf persons. The best known and at present probably the best understood dwarf is the ordinary thyroid cretin. This individual in the typical case is largely infantile and almost completely arrested in a state of development comparable to early childhood. The condition is definitely known to be due to an extremely defective or absent thyroid gland, and is very characteristic and readily recognized in spite of the various racial groups or even animal species among which it occurs. It would seem to be a definite developmental affair. There is no genetic basis necessarily concerned yet it is not at all impossible that such conditions might arise from definite germinal causes.

Other types of dwarf, such as midgets and achondroplastics, are probably of somewhat more complex origin, and such dwarfs exist in typical form among dogs and among other of the lower animals. There is an hereditary background for their condition and such animals may be bred with a high degree of constancy, yet the expression of the condition is quite variable and rigid selection is constantly necessary to maintain a fixed quality of the stock. The King Charles Spaniel and the Pekingese breeds of dogs are midgets with considerable achondroplasia, and these also show rather marked exophthalmic conditions. The thyroid and other glands of internal secretion in these dogs show certain peculiarities in their histological structure and the function of the glands is considerably disturbed. The general modified structure and shape of the animal results very probably from these modified internal secretions, and yet the peculiar condition of the glands of internal secretion is very likely inherited in either a direct or secondary way. In other words, it seems at present that these dog breeds actually inherit a peculiar gland modification and, as a result of this modification, their entire growth pattern is distorted and modified. Their physiological and psychological performance is also peculiar, and quite characteristic of the definite individual type or breed. The breeds of dogs are known as groups to be either gentle or shy,

kind, or irritable and snappy, stupid or intelligent, as the race may be. Persons having known one fox-terrier will know much about all fox-terriers but would find a very different character and behavior for a pointer, a bull-dog, or any other breed.

The French bull-dog and the British bull-dog show marked achondroplasia associated with different degrees of dwarfism. The causal factors here are quite similar to those just mentioned. These animal types exhibit very characteristic reactions which distinguish them more or less from the ordinary dog breeds, such as pointers and setters, in a great number of ways.

The point of particular interest to us is that the type peculiarities exhibited by these dogs are very closely comparable to the peculiarities found in human individuals of these same general types.

Among the dogs, gigantism is shown by the Great Dane, St. Bernard, Newfoundland, and others, and here, as in the human being, gigantism is very commonly associated with acromegalia. It would seem both in dogs and man that dwarfism and achondroplasia like gigantism and acromegalia are usual combinations. Here again among these giant dogs, such as the St. Bernard, one finds general characteristics and behavior closely suggesting that of the human acromegalic giant. The voice and disposition are actually strikingly similar.

A discussion of these extreme types might be carried still further, but it seems quite evident I believe from these few examples that the nature of the type or constitution in these cases is definitely associated with somewhat peculiar and modified growth conditions probably brought about in response to altered glandular reactions. The cause of this glandular alteration may have been primarily genetic. Here again one finds all gradations from these extreme glandular conditions back to the ordinary normal individual. If we examine more carefully the so called normal individuals, good observers may frequently note slight indications of the conditions considered above. The structural expression of individuals oscillates between certain delicately balanced growth tendencies which are greatly influenced by the conditions under which the individual develops.

In studying both embryonic development and postnatal growth I have been led to believe that the rate at which growth or development

occurs is a most important factor in determining the type and quality of the resulting structure. An individual that grows and differentiates rapidly, in the end shows a slightly different pattern from another which grows and differentiates more slowly. The rate of growth is no doubt dependent upon the rate of metabolism or rate of oxidation in the particular individual and, as far as our present knowledge goes, the one organ in the body having most to do in the long run with the rate of metabolism and growth is the thyroid gland. It may be that the slight differences in the activity of this gland have more or less to do with differentiating individuals into constitutional types.

When we study human beings as a group we find after careful inspection and on the basis of extensive anthropomorphic data that there tends to be in general two quite clearly contrasted types. The literature of anthropology indicates with surprising repetition that almost all anthropologists have originally recognized two human types. Roughly speaking, these are the long heads and the round heads. It is also true that when anthropologists have gone further with their studies they have become confused and have recognized in addition to the two original types a great number of other so-called types. When we look at the situation from a simple biological and developmental standpoint it seems easier to consider all the intermediate types as hybrids or mixtures of the two contrasted groups. A few years ago I attempted to point out the various contrasted characters in the two types and suggested that these simple differences in growth and development might result from slightly different metabolic rates in the two groups. This difference in rates of development was further associated with the thyroid activity of the individuals and this, in turn, might be decidedly influenced and affected by the nature of the environments in which the persons chanced to live for many generations. In general, it seems that all old and more or less sedentary races residing near the coast lines tend in type toward what is designated as the linear or high thyroid type, while the midcontinental people far removed from the sea and the source of iodine tended in the majority of cases to show a more rounded condition, a physiologically low thyroid or lateral type.

Since so many investigators in different fields have recognized these two types among human beings it seems strongly probable that such individuals actually exist and are typically differentiated from one

another. The differences between the two types are not only shown in many measurable morphological characters, but are equally evident in their physiological reactions and certain psychological tendencies. These types have also been recognized by psychiatrists, who have designated certain distinct differences between them, as introverts and extroverts, schizophrenic and cyclothymic and by numerous other terms.

The question of immediate connection and interest is whether, if these types do exist, they show different tendencies or diatheses towards the different diseases. Various clinicians from time to time have attempted to show that there are definite disease tendencies associated with certain type differences. Much of this work has been quite unsatisfactory, being very largely intuitive and impressionistic in nature. There is very little actually good quantitative data for consideration.

Recently, Dr. George Draper in New York has been conducting a study of various disease group individuals. He has not arranged the patients according to what might be considered type but has taken all individuals that actually showed a given disease and grouped these together. The measurements of the several groups have been compared. Many of his results are very important and are of considerable interest. The group comparisons often lend themselves, however, to further and different interpretations from those which Dr. Draper has pointed out. From this study of six different diseases, his curves and figures seem to indicate that only two of the disease groups are probably composed of a definite human type. The other groups are quite mixed in their characters and are probably composed of what one might term type crosses or hybrids. These disease groups differ from one another in more or less irregular ways and are not uniformly contrasted. It must always be recognized that a certain constitutional condition may show the diathesis for a particular disease entirely aside from the actual type of the individual. Draper makes no attempt to check against this fact. We really have few facts to indicate that the constitution as such is evidenced in a definite way by particular physical measurements. A suprarenal depression, for example, may considerably modify constitution without altering physical measurements. Such conditions must be recognized by morphological appearance and the peculiar physiological reactions.

Draper's group that suffered from gall-bladder disease seems from the measurements to be composed largely of lateral type individuals, and the contrasted group exhibiting gastric or duodenal ulcer seems to be quite uniformly composed of linear type persons

Members of these two disease groups are quite consistently contrasted with one another throughout the various measurements and indices which Dr Draper has employed. Of course, it is not certain that all of his measurements or indices actually have any value or significance for type distinction since such a value for many of them has not been established. Certain physical proportions might readily be common to the two types just as hair and eye color are. It would not be expected, therefore, that these two groups should contrast in every way in which Draper has compared them, but certainly in many ways, and in all of those thought to be the most reliable qualities for type distinction they are definitely contrasted. Even to fine detail, such as toothpattern and hand and nail shapes, the ulcer group and the gall-bladder group exhibit the characteristics which have been pointed out by various investigators for the linear type and the lateral type respectively.

Sex of course is one of the most important factors in influencing both the constitution and the type of the individual, and very probably sex plays an important part in disease tendencies. Sex differences in the inheritance of haemophilia and other diseases indicates the importance in constitution of sex composition. As I have recently pointed out, the significance of sex constitution is also strikingly shown by the direction of the morphological changes which follow the removal of gonads in mammals and birds. Among the mammals where the female is believed to be homozygous for sex, having in her cells two X chromosomes, and the male heterozygote having only one X, the castrated or spayed individual as the case may be approaches in its general structural trend the female or homozygous sex. While among the birds with the male instead of the female homozygous for sex, the castrated and spayed individuals approach in their structural changes the general male appearance instead of the female.

It is interesting to find that in Draper's ulcer group which is composed largely of the typical linear individual, the female is very rarely included. This disease would seem to be in the large majority con-

finer to males. The linear type is rarely so fully developed or so well expressed by the female as by the male. In brother-sister groups, for example, the cephalic index is almost invariably higher among the females than among the males, and the female is more often rounded or lateral in her general structure than is the same class male. If gastric ulcer is a linear type disease then females might rarely show it as they are not usually of the pronounced linear type. On the other hand, it was found that in the gall-bladder disease group, the females predominated and the males of this group were rounded, fat, avirile individuals. Here again the round type is more fully expressed by the female than by the male in a mixed population. The general metabolism of the female is probably lower than for the male, as is indicated by her structural condition and reaction, although the difference may not be of such a magnitude as to be momentarily measured by the calorimeter.

The only other quite typical disease group shown by Draper's measurements was a small number of acromegals. These of course are readily differentiated by ordinary morphologic criteria. The pernicious anemia group tended in their measurements very decidedly to approach the acromegals. They had very large subcostal angles and had an average profile that tended toward the acromegalic picture. These anemic persons may by some possibility be a peculiar deviation from the bone growth state of the acromegals. Both conditions may have some connection with calcium metabolism, and blood disturbance and bone disturbance in this way may be somehow interrelated.

It is most difficult at the present time to give any clear-cut or definite treatment of the relationship between human constitution and certain disease conditions. However, our present knowledge of inheritance and development along with a clearer understanding of the actions of the internal secretions in affecting body growth and form give present investigators a great advantage over earlier workers in understanding the relation of constitution to disease. The fundamental thing in this problem is in the first place clearly to determine the controlling elements in the development and differentiation of human constitutions. Until we actually understand the causes on account of which one constitution differs from another, it is most difficult to understand what their actual disease reactions mean. If there is any

direct connection between the constitution or the type and certain disease inclinations it then becomes highly important to devise more clean-cut scientific methods for distinguishing type. Type cannot be designated intuitively with actual reliability and there must be established some quantitative basis on which it may be clearly diagnosed. We must determine which are the important characteristics and features to be measured, remembering that soft parts may frequently be as characteristic as bony structures though not so easy to study and hence their neglect at the present time by anthropologists in general.

The entire subject of constitution, therefore, is one urgently demanding study and investigation. An initial appreciation of extreme types and large deviations from the normal along with the way in which these function, and react to disease, will give a more scientific appreciation of minor deviations and the normal types themselves. Such knowledge will be of value in both preventive and curative medicine. This need not in any sense mean that persons able to distinguish types may further predict the kind of diseases that a given individual will some day develop. The hope is rather more in the direction that when type is clearly known we shall be better able to understand how a patient will react to a particular disease.

An appreciation and understanding of the patient is certainly one of the greatest advantages the physician can hold in his effort to control and alleviate disease. The most important element in the complex situation of disease is the actual human individual involved and all effort and study towards an understanding of this element will scarcely be energy misdirected.

#### BIBLIOGRAPHY CONSIDERED<sup>2</sup>

- BAGG, H J, AND LITTLE, C C. Hereditary structural defects in the descendants of mice exposed to Roentgen-ray irradiation. *Am Jour of Anatomy*, vol 33, p 119-144, March, 1924.
- BARDEEN, C R. The height, weight index of build in relation to linear and volumetric proportions. *Carnegie Inst Contr to Emb*, No 46, 1920.
- BAUER, J. *Die Konstitutionelle Disposition zu inneren Krankheiten*. Berlin, 1921.
- CUSHING, H. *The pituitary body and its disorders*, Philadelphia, 1912.
- DRAPER, GEORGE. *Human constitution a consideration of its relationship to disease*. Saunders, Philadelphia, 1924.

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<sup>2</sup> For more complete list see Bauer, 1921.

- DI GIOVANNI, A Clinical commentaries deduced from the morphology of the human body London, 1919
- KEITH, A The evolution of human races in the light of the hormone theory Bull Johns Hopkins Hospital, vol 33, 1922
- KRAUSE, FR Allgemeiner und spezielle Path—der Person Klinisch Zygologie Leipzig, 1919
- KRETSCHMER, L Körperbau und Character, Berlin, 1921
- STOCKARD, C R Developmental rate and structural expression an experimental study of twins, "double monsters" and single deformities, and the interaction among embryonic organs during their origin and development Am Jour of Anatomy, vol 28, pp 115-278, January, 1921
- STOCKARD, C R Human types and growth reactions Am Jour of Anatomy, vol 31, pp 261-288, January, 1923
- STOCKARD, C R The significance of modifications in body structure Harvey Soc Lecture Series 1921-22, pp 23-64, Lippincott, 1923
- STOCKARD, C R The Gonads and Sex Physiology Proc Congress Phys and Surgeons, Washington, May, 1925
- STOCKARD, C R, AND PAPANICOLAOU, G N Further studies on the modification of the germ-cells in mammals the effect of alcohol on treated guinea pigs and their descendants Jour of Exp Zoology, vol 26, pp 119-226, May, 1918
- WRIGHT, SEWALL, AND EATON, O N Factors which determine otocephaly in guinea pigs J Agri Res, 26, 1923





# CEREBRAL BIRTH INJURIES AND THEIR RESULTS

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## I INTRODUCTION

A very extensive literature is to be found on the subject of birth injury of the central nervous system. Even in the last few years a number of important contributions have been made to the understanding of this important problem. The various types of intracranial lesions which may occur in the passage of the infant through the birth canal have been described with a detail and accuracy which leaves little to be desired and a very good understanding of the causes which lead to their production has been attained. On these pathological and obstetrical phases of the subject there is little to be said, because a very substantial agreement has been reached by most authorities. On the other hand, when we turn to the consideration of the late results of such birth injuries we find little exact information and the greatest difference of opinion. All types of congenital paralyses, athetosis, epilepsy, amentia and even hydrocephalus have been attributed by various authors to birth trauma often without the slightest evidence. It is the purpose of this paper to attempt a more exact definition of the group of true cerebral birth injuries. This work is the outcome of some unpublished experimental investigations which the writer has performed in association with Dr Charles Bagley.

The material on which the following studies are based was obtained almost entirely from the records of the Harnet Lane Home for Children by the courtesy of Dr John Howland. Case histories are also included from the records of the Surgical Department by permission of Dr Walter Dandy, and from the Obstetrical Department by permission of Dr J Whitridge Williams. I am indebted to Dr W G MacCallum for permission to include the pathological material.

The frequency and importance of birth injury is easily demonstrated by a few figures. One of the first important contributions to the morbid anatomy was made by Weyhe (1) in 1888. He published the autopsy findings of 959 still-born babies. Intracranial hemorrhage was found in 122 of these. Spencer (2) found hemorrhage in 40 per cent of his cases, Schott (3) in 30 per cent, Deluca (4) in 36 per cent, Schafer (5) in 20 per cent of 680 cases, Archibald (6) in 43 per cent, Warwick (7) in 43 per cent, Pierson (8) in 44 per cent, and Crothers

(9) in 65 per cent. Even higher percentages of intracranial hemorrhages are found in exceptional conditions such as breech delivery or prematurity. Ylppo (10) found injury of some degree in 90 per cent of premature infants. It is probable, however, that authors who find high percentages of intracranial hemorrhages include many small lesions which do not contribute to death. Holt and Howland (11) in summary of the figures obtained at the Sloane Hospital in New York state that about one-third of the deaths at birth, or in the first few days, are due to complications of labor.

There is some evidence that intracranial hemorrhage occurs in babies who survive and who may even show no clinical signs of birth injury. Weyhe, Doehle (12), Kundrat (13) and others have found old blood pigment in the meninges of children up to nine months of age who have given no evidence of birth injury at the time of birth. Recently Sharpe (14) has published the results of routine lumbar puncture in five series of 100 new-born babies each. In most cases the spinal fluid was removed in the first twenty-four or forty-eight hours. An average of 9 per cent of all new-born babies had bloody fluid. Very few of these showed any clinical signs of birth injury. Hines Roberts (15) has also performed lumbar puncture routinely on 423 colored babies and found blood in 60 fluids, or 14 per cent. Only 26 showed clinical signs of cerebral lesions and of these 12 died. It is obvious that these figures can not be accepted as conclusive, because it is not always possible to distinguish bleeding caused by the needle from fresh blood already in the spinal canal. It would seem preferable to defer lumbar puncture until the third or fourth day when any blood resulting from a birth injury would be tinged yellow and so easily recognizable. Nevertheless, these figures are not to be lightly disregarded as both authors have taken into consideration the causes of error and their figures are in substantial agreement. It is evident that intracerebral and subdural hemorrhages will not always reach the spinal fluid. In fact, blood in the ventricles or the anterior sub-arachnoid space may not reach the spinal fluid at once.

In summary, the conclusion seems justified that a very large percentage of babies dying at birth, or within the first two weeks, show intracranial hemorrhage at autopsy. In only about one-third of the cases, however, is this hemorrhage extensive enough to cause death.

There is some evidence that a small percentage of new-born babies, who seem normal, or at most show mild signs of intracranial hemorrhage, have blood in the spinal fluid.

## II. PATHOLOGICAL ANATOMY OF CEREBRAL BIRTH INJURY

### A. EARLY

A great variety of lesions has been ascribed by many different authors to birth injury. Weyhe described 122 cases of intracranial hemorrhage in the new-born. In 80 cases the bleeding was subdural, in 56 subarachnoid, intracerebral in 35, and intraventricular in 21. McNutt (16) found hemorrhages over the convexity in 8 cases and hemorrhage at the base in 2. Spencer reported bilateral hemorrhages over the convexity in 29 cases and unilateral in 20 cases. In 35 cases the hemorrhage was at the base and 7 times into the ventricles. Only 1 case showed hemorrhage into the substance of the brain. Warwick's cases showed bleeding over the convexity in 13 cases, bilateral in 7 and unilateral in 6, into the dura mater in 2, over the cerebellum in 1, and into the ventricles in 2 cases. In 2 cases of meningeal hemorrhage there was some softening under the clot. In no case was there any primary intracerebral bleeding. In summary she states, "All authors agree on the preponderance of bleeding over the cerebrum, usually limited to one side." Cushing (7) stated in 1905, "All extensive hemorrhages I have seen have been limited to one hemisphere and I am inclined to think the unilateral form is more common."

Holt and Howland's text book describes the findings as follows:

The hemorrhages may be large or small. If small, they are frequently multiple and are found scattered over the convexity. Large hemorrhages may be at the base or at the convexity. Convexity hemorrhages are rarely limited to one hemisphere, although one side may be much more affected. It is usual for the blood to gravitate towards the base and become diffused. Hemorrhages between the dura and the skull may be said never to occur except when associated with fractures.

In large hemorrhages the brain substance is softened and in places may be quite disintegrated. Hemorrhages into the membranes of the upper part of the cord are found in a large proportion of fatal cases.

Beneke (18) and several others have emphasized the frequency of

hemorrhage at the base and in the posterior fossa Sietz (19) has claimed that the bleeding is at the base in half of all cases

Schwartz (20) has found intracerebral hemorrhages and necrotic areas in a large percentage of children dying in the first six months of life The most common lesions were petechial hemorrhages and minute necrotic areas in the central white matter and basal ganglia around the third and lateral ventricles These are definitely related to the distribution of the tributaries of the vein of Galen, the vein lateralis ventriculi, vein choroids and the ventricular branch of the vein basalis Such lesions are usually minute, but very extensive destruction of the central white matter and basal ganglia may result In rare cases one or both hemispheres may be partially destroyed He also describes several cases with cortical softenings which he relates to meningeal hemorrhages In addition to these gross lesions Schwartz found evidence of a diffuse destruction of nerve tissue in a large percentage of infants Brains which seemed normal grossly showed on microscopic examination numerous fat-laden phagocytes scattered throughout the brain as well as in small foci Schwartz insists that the presence of phagocytes is always indicative of a pathological process and they are not to be found in new-born animals, whose brains are protected by solid skulls Fisher (21) and Siegmund (22) have described similar lesions

Extradural bleeding, always associated with fractured skull and usually with laceration of the brain, has been described by Archibald and Ballance (23)

Crothers (24) and Pierson have shown that injuries to the spinal cord and hemorrhage into the spinal canal with, or without, fracture of the spine are not uncommon especially in breech extraction

Intraventricular hemorrhages were described by Ballantyne (25) and Eastman (26) Hemorrhages into the retina have been noted by Stumpf and Sicherer (27), Paul (28), and Jacobs (29) in from 20 to 50 per cent of all new-born babies Voss (30), has been able to demonstrate bleeding into the inner ear in some cases

In recent analysis of the autopsy findings in 80 cases of still-birth or neonatal death, Capon (31) gives the following sources of intracranial birth hemorrhage

- 1 Small tentorial vessels coursing along the fibers of the tentorium may

be torn, the blood then collects in a film upon the upper surface of the cerebellum or upon the upper tentorial surface draining posteriorly around the occipital lobes.

2 Vena Magna Galeni, which is frequently distorted during the moulding of the head, may rupture at the point where the straight sinus is formed. The blood collects posterior to the mesencephalon and drains downwards around the cerebellum, pons and medulla.

3 Cerebral veins, near their terminations in the superior longitudinal sinus, may be injured. The effused blood flows downwards in the subdural space. Usually the hemorrhage is unilateral, but sometimes it is bilateral.

4 Superior longitudinal sinus, transverse sinus and straight sinus. It is only in the most severe types of birth-injury that such examples are found. The infant is almost invariably stillborn.

5. The internal cerebral veins, for instance the choroidal veins, may be damaged. These examples are rare, and are found almost exclusively in stillborn premature infants. The blood-collection may occupy the lateral, third and fourth ventricles, blood is also frequently found in these cases within the spinal membranes.

In summary we may say that in autopsies on the new-born large intracranial hemorrhages are frequently found. These are usually subdural, less often subarachnoid, and are situated with about equal frequency over the convexity and at the base. When the bleeding is over the convexity it is bilateral in about one-half the cases, but in most of these cases the amount of blood is unequal on two sides. Generally the blood diffuses throughout the subdural space and no softening of the cortex occurs, but local hematomas may occur and cause cortical softening. At the base large hemorrhages spread promptly throughout the meningeal spaces. Minute intracerebral hemorrhages are not uncommon in the central gray matter and brain-stem, and even large extravasations into the substance of the brain are sometimes found. Diffuse degenerations and focal necroses under the ependyma may be demonstrated in some cases. Fracture of the skull with extradural hematoma and fractured spines with injury to the spinal cord are not rare. Retinal and inner ear hemorrhages may be demonstrated.

## B LATE

There does not seem to be any general agreement among neuropathologists about the late pathological anatomy of intracranial birth hemorrhages. A great variety of lesions has been ascribed to this cause without any proper evidence. Indeed, the same end result may be due to several initial processes so that it is often impossible to distinguish between prenatal, natal and postnatal disease. The most important problem is the outcome of the very common subdural, or subarachnoid, hemorrhage over the convexity. Buzzard and Greenfield (32) say vaguely, "Such extravasations (subdural) are, according to some observers, the cause of some cases of infantile hemiplegia or diplegia. The results of intracranial hemorrhage, whether subdural or subarachnoid in cases which survive are very similar. The coagulum is partly absorbed and partly organized so scar tissue, with or without the presence of cysts, forms the permanent remains" (11). Sachs (33) states that chronic "meningoencephalitis" sclerosis, cysts and partial atrophies are the late results of meningeal hemorrhages and Holt and Howland are in essential agreement with this view. It seems probable, however, that some of the cases which were formerly described as examples of "meningoencephalitis" are really properly classified as "atrophic lobar sclerosis" which is unrelated to birth injury.

In discussing the late results of meningeal hemorrhage it seems helpful to distinguish between diffuse hemorrhages in the subarachnoid and subdural spaces, and local or encapsulated hematomas. It is probable that hemorrhages which diffuse do little damage to the cortex and either cause death from increased intracranial pressure or are absorbed without leaving any lasting injury to the cortex. Blood extravasated into the subarachnoid space is rapidly absorbed and usually does not leave any marked changes in the leptomeninges. The writer has examined the brains of two patients who had suffered repeated intraventricular hemorrhages over a period of a year in one case and two months in the other. In both cases there was merely some yellow staining and a scarcely perceptible thickening of the pia arachnoid. Yet there had been large amounts of blood in the spinal fluid. Symonds (34) mentions the case of a man who survived



subarachnoid hemorrhage and died of an intracerebral hemorrhage several months later. At necropsy no evidences of the first hemorrhage could be found. It is well known that any considerable amount of blood in the subdural space is organized and leaves a fibrous membrane under dura. This fact is supported by clinical experience with various types of "hemorrhagic pachymeningitis" and by the results of experiment. Putnam and Cushing (35) state that when blood is injected experimentally under the dura it is organized from the dural surface and a fibrous, cystic membrane remains attached to the under surface of the dura. It has been pointed out in the preceding section that meningeal birth hemorrhages are usually in the subdural space and even in case the blood ruptures into the subarachnoid spaces the major part of the blood remains under the dura. It is evident, therefore, that we may expect to find evidence of old meningeal hemorrhage in the subdural space.

It is a common observation among surgeons that the brains of epileptics and diplegics show opacities of the pia-arachnoid and collections of fluid in between the sulci. Sharpe (36) states that this is the result of a meningeal hemorrhage at birth which has been partly organized. This appearance may be deceptive, however, and 2 cases are included in this paper which showed an apparent thickening of the pia-arachnoid at operation, but at autopsy the meninges were grossly and microscopically normal. It seems probable that this apparent thickening is really merely a meningeal edema, and not to be regarded as in any way the result of a birth injury.

Campbell (37), Tredgold (38), and Cushing have described localized cortical defects and scars which they attribute with reason to localized meningeal hemorrhages produced by birth trauma. Tredgold gives a good description of a lesion in the brain of an epileptic with right hemiplegia which dated from birth. The patient died at the age of thirty-three. At autopsy the lesion was confined to a triangular area over the left hemisphere with its base at the great longitudinal fissure and its apex at the anterior part of the Sylvian fissure. Over this area the pia-arachnoid was opaque and thickened and could not be removed without decortication. The underlying convolutions were somewhat distorted and atrophied. Microscopic examination showed a diminution of nerve cells in the affected areas and a secondary proliferation

of glial tissue The opposite hemisphere was normal and no recent degeneration could be demonstrated by the Marchi method In the cord the motor path from the left hemisphere was diminished and sclerotic The dura mater was normal Campbell writes as follows

In addition to the microgyrous condition affecting idiots, described in the foregoing section, there is one which is very common, and though more frequent in the parietal and occipital lobes than elsewhere, is not restricted to any particular part of the brain The diseased area varies in extent and is represented by a small nucleus of puckered and contracted, or wholly destroyed gyri surrounded by others which are attenuated and sclerosed, but not deformed There may be more than one lesion, and in any case considerable cerebral deformity and asymmetry results I have seen many cases and the distribution of the lesions and the constant signs of postnecrotic destruction in the center of the area suggests a vascular lesion at birth or soon after

Cushing shows an illustration of a small defect in one paracentral lobule causing paralysis of one leg This he says resulted from birth injury

The possibility that meningeal or intraventricular hemorrhage may result in organization and obstruction of the aqueduct of Sylvius or the subarachnoid spaces and so cause hydrocephalus has been suggested The discussion of this problem will be reserved for a later chapter Suffice it to say here that any large amount of blood in the meningeal spaces will invariably cause a severe reaction, increased intracranial pressure and, in infants, enlargement of the head

One more condition must be mentioned among the possible late results of meningeal hemorrhage Schwartz, Burham and Gerstenberger (39), Doehle and many older authors, have suggested that "hemorrhagic pachymeningitis" of infancy might bear some relation to birth injury This problem is a very intricate one and can not be adequately discussed here However, Putnam and Cushing in their interesting paper on "Chronic Subdural Hematoma" have shown that in cases of traumatic subdural hemorrhage large endothelial lined spaces form under the dura and eventually become connected with the capillaries and filled with blood These structures are very fragile and, it is believed, that they may rupture and cause the hematoma to

grow It is possible that a slight injury to the head of a child with such a hematoma as a residuum of birth injury might result in further extravasation and the development of clinical symptoms Burham and Gerstenberger believe that there are two factors involved, birth injury and a second injury later which may be slight This view is not universally held and there is some evidence against it It is merely mentioned for the sake of completeness

The end result of the less frequent intracerebral hemorrhages is more clearly understood We would expect to find intracerebral cavities containing yellow pigment usually asymmetrically situated and sometimes unilateral A typical example of this type of lesion is described in Holt and Howland's Text Book

Schwartz has been able to show that the periventricular hemorrhages and necroses which he has found in so many still-born infants result eventually, if the infant survives, in porencephalic cavities usually separated from the ventricular lumen by a thin membrane and crossed by trabeculae Such cavities are often bilateral and nearly symmetrical and are usually considered examples of developmental defect Schwartz, however, shows convincing illustrations of all stages in their development He also shows beautiful examples of peripheral porencephalus resulting from cortical birth hemorrhage Even the cases which show replacement of a whole hemisphere, or both hemispheres, by a thin walled sack, Schwartz believes, are due to birth injury Fischer and Siegmund subscribe to these statements

Two types of porencephaly, therefore, result from birth injury, the periventricular type produced by hemorrhage from the vein of Galen and the cortical type due to superficial injuries These are properly examples of "false" porencephaly and it is customary to distinguish such cases from "true" porencephaly which is regarded as representing a defective development of the cerebral hemispheres Various criteria are given for the distinction between the "true" and "false" types, but Collier (40) states that these are not sufficient and the differentiation is not always possible on anatomical grounds

In summary, we would expect to find as the end result of former intracranial hemorrhage at birth the following conditions Subdural hemorrhages might be expected to leave a fibrous membrane under the dura mater containing traces of old blood pigment Diffuse sub-

arachnoid bleeding is probably absorbed without causing any permanent lesions except possibly some thickening of the meninges at the base. Encapsulated supracortical hematomas, it seems probable, result in local atrophy and sclerosis with thickening and possible cyst formation in the overlying meninges. These changes should be unilateral in at least half the cases and usually asymmetrical. Intracerebral cavities (false porencephaly) of two types are to be recognized, those resulting from cortical hemorrhage and containing old blood pigment in their walls and those, described by Schwartz, resulting from periventricular extravasations often bilateral and separated from the ventricle by a thin membrane. Some authors state that sometimes hydrocephalus and "hemorrhagic pachymeningitis" are related to intracranial hemorrhage at birth.

### III CAUSES OF CEREBRAL BIRTH INJURY

The preeminence of trauma among the causes of intracranial hemorrhage in infants is now almost universally accepted. Obviously any condition which increases the stress which the foetal head sustains in its passage through the birth canal will increase the chances of injury. Contracted or malformed pelvises, rigid soft parts, precipitate or prolonged labor, abnormal presentation, high forceps deliveries, breech extraction, or over-large foetal heads are all common factors which predispose to birth injury. These considerations are, however, outside the scope of this paper and will not be discussed further.

Illuminating analyses of the mechanical factors involved in birth injury have been published recently by Holland (41), Greenwood (42) and Ehrenfest (43).

The commonest type of hemorrhage which is found over the convexity in the subdural or, less frequently, the subarachnoid space is due to over-riding of the parietal bones and tearing of the tributary veins to the longitudinal sinus. Cushing has been able to demonstrate this lesion in two of his cases. He points out that these veins are very fragile in the infant and unsupported in the subdural space by Pacchionian granulations and connective tissue as in the adult. Moreover, they stretch between their fixed attachment to the sinus and the relatively movable brain. In some cases the longitudinal sinus may be torn and thrombosed.

Ehrenfest states that infrequently a similar over-lapping of the parietal bones over the occipital bone and tearing of the lateral sinus or the veins, which empty into it, may occur, more especially in cases of breech extraction

Distortion of the head by excessive moulding is an even more important cause of dural tears Beneke showed in 1910 that compression of the head in one diameter results in shortening of that diameter and a compensatory increase in some other diameter. Since pressure on the fetal head is usually antero-posterior or lateral or both, it is evident that the vertical diameter must be increased This change in configuration is resisted by the dural ligaments, the falx and the tentorium, which are stretched and if the tension is great enough may be ruptured Tears in the tentorium are very common and are most frequent near the insertion of the falx Often the straight sinus or some of the larger veins are torn and a fatal hemorrhage at the base or over the cerebellum occurs If the antero-posterior diameter is increased too much, the falx may tear, although this is not common Beneke described 14 cases with tentorial tears which he had discovered in one hundred autopsies on still-born babies He also published in detail his valuable method for the study of intracranial pathology Beneke's work was soon confirmed by Sietz who found tentorial lacerations in half his cases Recently Holland has given a lucid exposition of the forces concerned He confirms and amplifies Beneke's observations In his series of 167 autopsies, he demonstrated tentorial tears in 81 and laceration of the falx in addition in 5 cases He showed that permanent asymmetry of the head, the so-called oblique head, may result from tears in the tentorium in cases that survive Greenwood has since made exact studies of infants' heads by plaster casts taken immediately after birth and again a week later He thinks that in normal vertex presentations the vertical diameter is not increased On the contrary it may be shortened with over-lapping of the parietal bones The antero-posterior diameter is, however, definitely lengthened In brow presentations and breech extractions he has shown the vertical diameter is always increased

Greenwood and Siegmund both think that the Schultze method of resuscitation may be a possible cause of dural tears

In an excellent analysis of the intracranial pressure changes in

breech delivery, Crothers has shown that this method of delivery imposes a great strain on the tentorium. He points out that the force of uterine contraction and manual suprapubic pressure both tend to compress the walls of the supratentorial chamber and consequently cause pressure on the tentorium from above, and that traction on the body, which he shows is transmitted in part to the spinal cord, tends to draw the medulla down. The result is rupture of the tentorium and possibly herniation of the medulla into the foramen magnum with injury to the vital centers and death.

The cause of the multiple extravasations from the vein of Galen and its tributaries is believed by Schwartz to be stasis due to vasomotor disturbances. Holland gives a much better explanation. He points out that the vein of Galen extends between the fixed sinus and the relatively movable brain. In the process of moulding the vertex is raised and the vein of Galen is sharply kinked and stretched. This will occlude the vein and may even cause rupture of the vein or its tributaries. Holland has been able to demonstrate actual tears in the vein in several cases.

Another factor to be considered in all cases in which there is laceration of the large veins or dural sinuses is the interference with venous drainage which results. This must cause congestion and edema and add to the intracranial pressure. Dandy (44) has been able to produce a low grade of hydrocephalus by ligating the vein of Galen near its junction with the sinus. The increase in intracranial pressure resulting from lateral sinus thrombosis is well known to otologists.

Cerebral concussion and edema must result from the compression and moulding which the fetal head is subject to in difficult labors. Greenwoods' casts show almost incredible distortions. "Shearing stress" as well as direct compression is to be considered. Schwartz believes that the diffuse destructive changes which he has demonstrated are due to trauma and it is possible that such changes may be the explanation of those cases which show signs of intracranial injury and pressure without any bleeding to be found at autopsy.

Prolonged compression of the trunk during breech delivery causes intense intracranial congestion by forcing blood out of the venous reservoirs of the chest and abdomen back through the incompetent valves of the jugular veins into the head and neck. In adults severe

compression of the chest has been known to cause the extraordinary picture of "traumatic asphyxia" (45) in which the most intense cyanosis of the head and neck may persist for several days. Convulsions may occur under these conditions

Multiple petechial hemorrhages in the brain and meninges, especially if associated with hemorrhages on the serous surfaces, are probably caused by asphyxia. Similar findings are seen in adults dying of suffocative asphyxia without head injury, and there is no reason to doubt that asphyxia may produce the same lesions in infants. There does not seem to be any clinical evidence that any recoverable degree of asphyxia unassociated with hemorrhage may permanently injure the pyramidal cells and yet spare the more resistant cells of the medulla. Nevertheless, Pike (46) and others have shown by experimental interruption of the cerebral circulation in animals that the cells of the medullary centers resist anemia longer than the cells of the cortex. The restoration of the cerebral circulation causes severe convulsions and if the animal survives it may show abnormal behavior, blindness and paralysis. No gross lesions are found in the brains of these animals when they are killed after several weeks, but microscopically necrosis of the cortical motor cells and degeneration of the pyramidal tracts can be demonstrated. There is no doubt that asphyxia increases bleeding from torn vessels by causing congestion, but there is considerable doubt whether it may produce rupture of large veins and considerable hemorrhage, unaided by other factors.

An important contributing cause of intracranial hemorrhage is prematurity. Couvelaire (48) found 18 per cent of premature babies born by easy spontaneous labors showed hemorrhages. Ylppo found intracranial traumatic lesions in 90 per cent of all premature infants. Most of these were unimportant, however. Paul states that the greatest incidence of retinal hemorrhages occurs in the premature. One-fourth of Warwick's cases of intracranial hemorrhage were in immature infants. Browne (48) states that intracranial bleeding occurs 16 times more frequently in premature infants than in full term babies. Raiz (49) discovered fatal hemorrhage in 23 per cent of premature still-born babies and in only 5 per cent of babies born at term or after eight months. Both Sharpe and Roberts agree that prematurity favors

intracranial hemorrhage In explanation for these facts Ylppo has proved that the cutaneous vessels of premature babies are abnormally fragile He applied suction to the skin and determined the pressure at which hemorrhage occurred In mature babies a pressure of 520 mm Hg was required, in premature infants only 150 mm Hg pressure caused rupture of the veins He states that 7 per cent of premature infants are either mentally defective or develop spastic paralysis Ehrenfest points out that the thinness of the premature infant's skull is a factor of importance in predisposing to excessive moulding and intraeranal injury, and Schwartz found that animals whose skulls are solid do not suffer birth injuries

The importance of prolonged coagulation time, which may give rise to hemorrhagic disease of the new-born, was first pointed out by Green (50) This factor has been emphasized by Warwick, Foote (51), Kaiser (52), Cruikshank (53) and Rodda (54) Warwick found gross hemorrhages in the viscera in 8 of her 18 cases of intracranial hemorrhages, and Rodda states that there were multiple hemorrhages in 20 per cent of her cases On the other hand some authors are inclined to attribute less importance to this factor Holt and Howland quote figures from Ritter and Townsend whose cases of hemorrhagic disease all together total 240 In only 4 out of this number did intracranial hemorrhage occur Sharpe and Roberts could find only 3 babies with prolonged coagulation time in their total number of 105 with bloody spinal fluid There can be no doubt, however, that spontaneous bleeding may occur in the skull from this cause just as it occurs in the abdominal viscera, and a delay in coagulation time no doubt will prolong the slow oozing from a small torn vessel until a large hematoma has accumulated

Syphilis and other diseases of the fetus probably play some rôle Brissaud (55) and Dejerine (56) have stated that syphilis favors intraeranal birth injury by causing prematurity Weyhe believed that 23 of his 122 cases of intraeranal hemorrhage showed signs of congenital syphilis Hedren (57), however, found only 3 cases of syphilis in autopsies on 700 infants, 9 per cent of whom showed intracranial bleeding Warwick did not find any signs of syphilis in her 18 cases Sharpe and Roberts do not consider syphilis important

Cases of intraeranal hemorrhage occurring in utero before labor



are not unknown Cotard (58), Sietz Gibb (59) and Osler (60) have described cases of this nature

#### IV. RESULTS OF CEREBRAL BIRTH INJURY

##### SIGNS OF BIRTH INJURY

The early signs of intracranial hemorrhage in infants are familiar to all obstetricians. Recent studies have been made by Cameron (61), Capon, Henkle (62) and Holland, but little of importance has been added to the descriptions of the older writers. If the hemorrhage is extensive, the child may be still-born. If alive, it may be deeply asphyxiated and difficult to resuscitate. The "blue" asphyxia is of little significance, and it has been estimated that this occurs to some extent in 90 per cent of all new-born babies. The so called "pallid asphyxia" is more serious. Crothers has shown that this is in reality vasomotor collapse due to medullary injury. If respiration is established, it may be noticed in the next few days that the child is sluggish and unresponsive, more rarely it may be restless. The cry is feeble and the child does not nurse. Respiration is slow and irregular and there is often some cyanosis. The pulse is usually slow, but may be feeble and rapid. If the bleeding is over the cortex, there may be local muscular twitching or general convulsions. Rigidity and retraction of the head are often seen. Unequal pupils, nystagmus, strabismus and even exophthalmos are described. The fontanels may bulge, but this is not always to be relied upon. Changes in the retina may be found. On lumbar puncture the spinal fluid is bloody and under increased pressure. It is not unusual to have the signs delayed until the fourth or fifth day, when the indications of increased intracranial pressure give evidence that an intracranial hemorrhage has been slowly accumulating.

It is well known that some intracranial hemorrhages give no obvious signs. Sharpe says that scarcely any of his 45 cases could have been diagnosed without lumbar puncture. Roberts noted clinical signs of birth injury in only 14 children out of the 48 that survived. I have already mentioned that Weyhe and Kundrat state that it is common to find evidence of old hemorrhages which have caused no clinical signs. Schule (63) refers to a baby who died suddenly at six weeks with a

large hemorrhage from a torn tentorium and Manton (64) gives the history of a similar case in which death occurred on the tenth day from an extensive hemorrhage coming from a tear in the longitudinal sinus. Neither of these babies had shown any evidence of birth injury.

It may be well to state here that all the signs of intracranial injury enumerated above may occur in cases in which no intracranial hemorrhage is found at autopsy. It is probable that the pathology in some of these cases is cerebral edema from cerebral concussion, or perhaps, congestion. Sharpe believes he can demonstrate increased intracranial pressure in these cases by the spinal manometer. I shall show later that children with congenitally defective brains may also show signs which simulate birth injury.

The overwhelming majority of babies who show definite clinical signs of intracranial hemorrhage die within a few days. In one series which I have personally investigated only 7 out of a series of 50 in which the diagnosis was made survived for two weeks. It is evident that lesions of the neuraxis between the tentorium above and the phrenic nucleus below will be fatal in almost every instance. Lacerations of the large veins and the dural sinuses are probably almost always incompatible with life. Moderate supracortical hemorrhages probably have the lowest mortality.

#### PHYSIOLOGY OF THE INFANTILE NERVOUS SYSTEM

This peculiar lack of signs associated with intracranial hemorrhage in the new-born will be more comprehensible if we consider the physiology of the infant's central nervous system. At term the cortex and its projection tracts are still partially unmyelinated, and, hence, it is generally assumed, are not functional. The pyramidal tracts do not become completely myelinated until somewhere between the ninth and twenty-fourth months of extrauterine life. The segmental apparatus of the brain stem and spinal cord is functional and probably already completely myelinated at birth. There is evidence that myelination of the various "association" tracts in the cortex continues for many years after birth. Two babies born in the maternity wards of J. Whitridge Williams, who showed all the reactions of normal babies including crying, nursing and vigorous movements, were found on necropsy to have been born without the cerebral hemispheres.

This observation is, in fact, a very old one and is attributed by Little to Ollivier. It indicates very strongly that the cortex plays no part in the normal activities of new-born babies. Pulse, respiratory rate, and temperature control are not well established at term. Tendon reflexes and the plantar reflexes are variable at birth and have no value in diagnosis as Burr (65) has shown. It would seem, therefore, that the normal activities of the new-born infant are all reflexes mediated by the brain stem and the spinal cord. However, the convulsions and local twitchings which sometimes result from cortical injuries, suggest that the cortex is not entirely insensitive to irritation.

Thus, it seems probable that the common signs of intracranial hemorrhage in infants result from involvement of the brain stem, either directly by bleeding into the posterior fossa, or indirectly by increase of intracranial pressure from the accumulation of a large hemorrhage above the tentorium. A localized hematoma over the cortex may compress and soften the cortex without giving any signs of its presence except, perhaps, some local twitching of convulsions. Respiratory disturbances without other evidence of intracranial injury have been attributed by Still (66) to small hemorrhages in the medulla, and Kirkwood and Meyer (67) have been able to demonstrate a small medullary hemorrhage in such a case.

#### LATE RESULTS OF INTRACRANIAL BIRTH HEMORRHAGE

It is quite certain that some few infants survive moderately large intracranial hemorrhages and afterwards show no clinical signs of cerebral injury. Numerous articles may be found in the literature advocating some type of operative procedure, subdural puncture or spinal drainage, and always including one or two histories of children who have survived intracranial hemorrhages and, strange to say, have not developed "Little's disease" afterwards. In each case this remarkable outcome is attributed only to the special treatment advocated by the author. Cushing (68) operated upon 9 babies with intracranial birth hemorrhage and stated in 1908, that the 4 who survived were all well. Most of these children had been under observation for over a year at that time. Gilles (69) reported 2 cases with complete recovery in children who were not subjected to operation, but were treated by lumbar puncture. Simmons (70) operated on a

child with intracranial hemorrhage who was quite well at the age of thirteen months. Green (71) reports 2 complete recoveries, one with operation and one with lumbar puncture. Lippman (72) described a case of meningeal hemorrhage in which only one lumbar puncture was performed. Nevertheless, the child made a complete recovery without residuum and developed normally. Brady (73) published 2 similar cases treated by spinal puncture. These children were well at the ages of three and fourteen months. Foote has followed a child who had a meningeal birth hemorrhage for four years and another for six years. Both these children are quite well. They were not subjected to operation. Rodda found 2 children who had shown blood in the spinal fluid at birth perfectly normal at the ages of four and ten months. Vaglio (74) reports 1 case of a child treated by lumbar puncture who is normal at six months. Munro (75) has published case histories of 9 children who survived intracranial hemorrhage and were well at the ages of one, six, nine, one, one, eight, eleven, eight and ten months. Most of these children were subjected to two lumbar punctures and no craniotomies were performed on the children who survived. Roberts does not believe that any of the 48 babies in his series who showed blood in the spinal fluid are going to develop diplegia, although the period of observation is still too short to be conclusive. The writer has been able to find records of three children who survived intracranial hemorrhages at birth and were well at the ages of six months, one year and nine months, and two years (see appendix A). In confirmation of these statements it may be mentioned that it is unusual for subarachnoid hemorrhage in adults to result in local cortical lesions. The writer has observed eight cases of primary subarachnoid hemorrhage all of whom recovered without any sign or symptom of cortical damage. One of these patients eventually had a recurrence and came to autopsy. No lesion of the brain was found.

Since the publication of Little's famous article in 1862 many diverse clinical syndromes have been attributed to the more severe birth injuries. Spastic diplegias, hemiplegias, monoplegias, congenital athetoses, epilepsy, idiocy, and hydrocephalus are the most important. Cerebral diplegia, most frequently called "Little's disease," is, however, considered the most typical example of the late results of birth injury. All these conditions will be discussed in the following sections.

## V. RELATION OF CEREBRAL BIRTH INJURY TO SPASTIC PARALYSIS

### CONGENITAL DIPLEGIA

This is the commonest type of congenital cerebral paralysis, occurring in the Harriet Lane Home records many times more frequently than congenital hemiplegia. It may be defined as a congenital condition of spastic weakness which affects the legs more than the arms or the legs alone. The most severe cases show general rigidity of the extremities and bulbar palsy. The mildest cases show only slight spasticity of the legs and a tendency to walk on the toes. These are, in fact, paraplegias. In hemiplegia and double hemiplegia it is the rule in infants, as well as in adults, for the arms to be more severely affected than the legs. These distinctions make the differentiation of diplegias and double hemiplegias possible in most cases. Diplegia is associated almost invariably with some degree of mental defect and not infrequently with epilepsy and microcephaly. Severe forms are evident at birth. Milder forms are not usually noticed before the age of six months. The tendency in some cases is towards limited improvement. If there are frequent convulsions the course may be slowly progressive. Choreiform, athetotic, flaccid and ataxic varieties are described, but are less frequent than the spastic type. It is evident that the postnatal progressive diplegias should be excluded from this group, although Collier has shown that they bear a fairly close relationship to some of the congenital diplegias. The distinction which Little made between rigidity and weakness has been supported by continental writers, but it is difficult, if not impossible, to maintain.

### *Historical*

In 1862 Little's (76) paper entitled "On the Influence of Abnormal Parturition, Difficult Labors, Premature Birth, Asphyxia, Neonatorum, on the Mental and Physical Condition of the Child, Especially in Relation to Deformities," appeared in the Transactions of the Obstetrical Society of London. It is evident from the following extract of that article that Little believed that asphyxia was the most important factor in the production of diplegia. He says,

Nearly twenty years ago, in a course of lectures published in the *Lancet*, and more fully in a Treatise on Deformities, published in 1853, I showed that

premature birth, difficult labors, mechanical injuries during parturition to head and neck, where life had been saved, following the act of birth were apt to be succeeded by a determinate affection of the limbs of the child, which I designated spastic rigidity of the limbs of new-born children, spastic rigidity from asphyxia neonatorum

Little did not attribute diplegia to gross hemorrhage, although this view is often attributed to him

McNutt (77) in 1885 was one of the first to ascribe diplegia definitely to meningeal hemorrhage. She described the anatomical findings in ten babies dying of birth injuries and some months afterwards, reported a case of diplegia which she believed had resulted from a meningeal hemorrhage at birth. McNutt's paper was presented before the American Neurological Society as a thesis for admission and attracted universal attention. Many neurologists accepted her views, preeminent among whom was Sir William Gowers (78), Marfan (79), Raymond (80), Taylor (81), Osler (82) and many others have since lent their support to her theory which is now held by most pediatricians and neurologists with certain notable exceptions. Recently Cameron and Osman (83) and Sachs (84) have declared their belief in the meningeal hemorrhage theory, but it must be admitted that they have failed to offer any convincing evidence to support their opinion.

Brissaud, in 1894, influenced by the high incidence of prematurity in diplegic infants, suggested that the determining factor was prematurity which interrupted the development of the pyramidal tracts. He excludes cases with mental defect and epilepsy. According to Brissaud, the pyramidal tract has just reached the medulla at the seventh month of fetal life and premature birth at that time will cause generalized rigidity. At the eighth month the pyramidal fibers have reached the thoracic region and arrest of growth will cause paraplegia. After birth the pyramidal fibers may still grow slowly, hence these cases tend to improve, even to recover. Marie (85), Dejerine, and Van Gehuchten (86) have subscribed to this view with only minor reservations.

Freud (87) stated in his elaborate monograph of 1897 that he was unable to find any evidence that diplegia was due to birth injury.

He believes that premature, precipitate and difficult labor and asphyxia are all the result of the same causes that produce the diplegia. He shows that cases of diplegia dating from birth sometimes occur in the same families in which post-natal progressive diplegias develop, and assumes that the causes are similar. He refers to cases reported by Freer (88), Krafft-Ebing (89), Newmark (90), and Peltzæus (91) in support of these statements. Freud distinguishes very clearly between diplegias and double hemiplegias. Hemiplegias and double hemiplegias result from gross lesions, often birth hemorrhages, diplegias are the result of degenerative processes.

In 1900, Collier published an exhaustive analysis of the cerebral diplegias, including both anatomical and clinical evidence. He subjects the meningeal hemorrhage theory to very pertinent criticism and concludes that the pathological process is that of a neuronc degeneration which is usually pre-natal and non-progressive, but may be post-natal and progressive. Some cases, he admits, may be due to congenital defect. With few exceptions his views are identical with those of Freud. More recently Collier (92) has again illuminated the subject with a vigorous statement of his original point of view. His arguments will be given in greater detail in the discussion of the pathology.

Thus, five principal theories have been advanced to account for cerebral diplegia, that it is due to asphyxia, to meningeal hemorrhage, to an arrest of development resulting from prematurity, to a degenerative process in utero, and to a congenitally defective development of the brain.

### *Discussion*

The reasons for connecting birth trauma and diplegia are not hard to find and a great deal is to be said both for and against this theory. We have seen that birth injuries are extraordinarily frequent, even in easy and apparently normal labors. It has been shown that although a great variety of intracranial lesions may occur, in infants born dead or dying soon after birth, one of the commonest lesions is a hemorrhage over the convexity near the midline so situated as to compress the cortical leg center. Such extravasations may be bilateral. Hemorrhage here can not diffuse so rapidly as at the base, where the subarachnoid spaces are larger, but is more apt to form an encapsulated hematoma.

and compress the cortex. It is an old observation that diplegic babies are commonly premature, and are often born by precipitate or prolonged labor, all conditions which we know predispose to intracranial hemorrhage. These infants are difficult to resuscitate, cry feebly, nurse poorly and, not infrequently, have convulsions, all of which are suggestive of birth injury. When it becomes evident, in a few months, that mental development is not progressing properly and that the child is diplegic, the conclusion that these symptoms are the result of birth injury is almost irresistible.

On closer scrutiny the evidence that diplegia is due to meningeal hemorrhage is not conclusive, and there are many facts that point to a pre-natal cause. I am not aware that any large series of cases with definite clinical signs of intracranial hemorrhage at the time of birth have been followed to their ultimate outcome. This, indeed, would be every difficult to do because almost all cases with severe signs die in a few days or weeks. I have been unable to find a single report of a case of true cerebral diplegia in which the occurrence of an intracranial hemorrhage at birth was established. The direct evidence is, therefore, unavailable. The fact that extensive cerebral lesions are found in infants that die promptly is no proof that lesions of similar magnitude exist in infants that survive. It is well known, moreover, that meningeal hemorrhage in adults usually does not injure the cortex. Even the demonstration of blood in the spinal fluid can not be accepted as always indicative of brain injury. If Sharpe and Roberts are correct in their estimate that about ten per cent of all new-born babies have blood in their spinal fluid, it is evident that in the vast majority of cases it does no harm. The frequent, but not invariable, occurrence of difficulty in establishment of respiration, feeble cry and poor nursing may just as well be attributed to a congenitally defective nervous system as to a birth hemorrhage. The same argument may be advanced to explain the convulsions. Congenital defects of the nervous system are not at all rare, and every obstetrician is familiar with the grosser malformations. Indeed, 25 per cent of all diplegics are microcephalic.

It does not seem probable that asphyxia alone without gross hemorrhage can be of much importance. Little himself says, "It is obvious that the great majority of apparently still-born infants, whose lives



are saved by the attendant accoucheur, recover unharmed from that condition" Manton states that he has been unable to connect asphyxia with paralysis or other abnormalities of the nervous system Buchardt (93) in a series of ninety babies deeply asphyxiated found only one abnormal later. Beatus (94) at Breslau came to the same conclusion Walter Hannes (95) has followed three series of 150 cases each The first group consisted of babies who were deeply asphyxiated and delivered by forceps, the second series consisted of babies not asphyxiated but delivered by forceps and the third included only babies normal in all respects After some years the largest percentage of abnormalities of the nervous system was found in the third, or normal group, i e , 3.4 per cent The first and second groups showed 3.2 per cent and 3.3 per cent abnormalities of the nervous system respectively

Brissaud's theory that prematurity is the important cause in the production of diplegia can not account for more than a certain percentage of all cases because far more than 50 per cent of cases are born at term Brissaud, indeed, restricted his group so as to exclude all cases which were not premature We shall see in the discussion on the morbid anatomy of diplegia that there is some pathological evidence to support his theory, that there is an arrest of development of the pyramidal tracts There is no doubt, however, that over 90 per cent of premature babies that survive complete the development of their nervous system in time, and it is well known that medullation continues long after birth under normal conditions

In the present imperfect state of our pathological knowledge of this subject, it scarcely seems justified to minimize the distinction between the congenital diplegias which tend to improve and the post-natal progressive cases, although Freud and Collier have shown that transitional cases occur However, it is impossible to explain all cases of diplegia on one basis and we shall see in the next section that several different pathological conditions underlie this clinical syndrome

### *Pathology of cerebral diplegia*

The cerebral lesions that have been found in cases of cerebral diplegia are not always the same, and a great difference of opinion exists about their significance Such cases come to autopsy long after the

active process has ceased and the end results may give little information about the original causes. The subject is further complicated by the fact that many authors do not give any accurate clinical classification of their cases.

Osler collected 31 diplegias and paraplegias. In 17 of these the pathological anatomy was available. In 3 cases bilateral porencephalic cavities were found. In the remaining 14 cases diffuse atrophy and sclerosis was the only finding.

Treud stated in summary of the large number of cases he had collected that the pathology of cerebral diplegia was a degenerative process and distinguishable from the lesions which result from birth injuries. He pointed out that the gross lesions sometimes described in diplegias could not serve to explain the symptoms which were due to neuronic degeneration demonstrable with certainty only with the microscope. Collier demonstrated in 1900 that the typical pathological picture was a diffuse symmetrical atrophy of both hemispheres with destruction of nerve cells and proliferation of glial tissue. The meninges are unaffected. In early cases the gross atrophy and gliosis are less evident and the degenerative process in the neurons is more conspicuous. The convolutional pattern of the hemispheres, which is established by the seventh month of fetal life, is usually normal but not infrequently shows evidence of interference in development long before birth. Sometimes the pyramidal tracts are absent, sometimes they are degenerated. Porencephaly of various types is found, but Collier very plausibly argues that these are cases of double hemiplegia, not true diplegia. He shows that the famous case reported by McNutt can not be in any way related to meningeal hemorrhage. Indeed, Welch, who made the pathological examination, states clearly that the process originated in the deeper layers of the cortex and involved the superficial layers least of all. Collier's own cases were all progressive post-natal cases and the pathology in these cases can scarcely be considered directly applicable to the problem of the congenital cases. In support of these statements Collier refers to autopsies by McNutt, Mane, Jendrassik, Warda, Mya and Levi, Sachs, Cotard, Schultze, Anton, Monev, Hennoch, Forster, Isambert, Becliterew, Russell, Robin, Friedman, Muratoff, Schmaus, Gee, Richardiere, Bournville and Brissaud, Dejerne and Solher.

Campbell describes the pathological condition which Freud and Collier believe is the basis of cerebral diplegia under the title of "lobar agenesis with sclerosis and microgyria" Buzzard and Greenfield employ the term "atrophic sclerosis," which they say gives rise to some types of idiocy, diplegia and microcephaly Their description is as follows

Macroscopically, the chief appearance is that of atrophy, either localized or affecting to a greater or less extent the whole brain substance In slight cases the convolutions when stripped of their meninges appear normal, but examination with a lens reveals here and there depressions or scar-like puckerings The surface may have a finely worm-eaten appearance In some advanced cases the convolutions may be irregular, atrophied, firmer than normal, and unlike healthy brain substance In extreme degrees of the process the convolution is represented by a thin leaf of fibrous substance, the so-called "parchment-like convolution" Sections of such areas show numerous small cavities in the gray matter The parts of the mid- and hind-brain associated with the sclerosed areas fail to develop, and the cerebral peduncles are smaller on the affected side Microscopically the condition is one of neuroglial overgrowth associated with degeneration of the neuron substance The process appears to affect primarily the deeper layers of the cortex, and spread thence to the underlying white matter and to the superficial layers of the cortex

The authors consider this condition a congenital abnormality due to some pre-natal morbid process

Hammarberg's (96) classical paper contained the description of 9 brains of idiots with various degrees of spastic diplegia In each case a congenitally defective brain was found In 4 cases there was complete amentia and severe spastic paralysis The brains showed only one layer of cortical cells much diminished in number These cells resembled the cortical cells of the fetus of five months In 2 cases with some degree of mental development the cortex showed the development of a normal child of about one year One of these children was severely paralyzed and its motor cortex showed very few giant cells The second child had much better motility and the giant cells were correspondingly more numerous Three more brains of children with slight or moderate amentia were studied Two of these 3 patients were diplegic and few giant cells were to be found in their motor

cortex The third child was not spastic and numerous giant cells were demonstrable in the motor area Greenfield and Buzzard say "Another type of developmental defect associated with cerebral diplegia is shown by those brains which present the features associated with the early months of fetal existence, and which do not show the division of the cerebral hemispheres into numerous convolutions" They give an illustration of a brain of this type

Ganghofner (97) has reported three cases of congenital diplegia in which the brain was grossly normal in every respect Microscopic examination revealed nothing abnormal, yet he believed that there was probably some decrease in the pyramidal fibers in the cord which he could not demonstrate The Betz cells in the motor cortex were normal Two valuable papers have been published by Spiller (98), one in 1898 and one in 1905 In all he describes 3 very instructive cases of congenital diplegia with autopsy All these brains were normally convoluted and showed no gross lesions One was under normal size Microscopic examination showed normal Betz cells in the paracentral lobule in each case, but in 1 case they seemed somewhat diminished in number The pyramidal tracts in the cord showed no degeneration, but in 2 cases the fibers seemed abnormally fine In the third case the pyramidal fibers seemed entirely normal, and Spiller could only conjecture that they did not reach the lumbar cord in normal numbers This could not be actually demonstrated, however Rhein (99) of Philadelphia has also contributed cases similar in every way to those described by Spiller The motor cortex was normal except for the absence of Betz cells The pyramidal tracts in the cord were abnormally fine but no degeneration could be found Biswanger (100), Gerlich (101), Otto (102) and Haushalter (103) and Collins have also described similar cases Many of these brains in which no definite anatomical basis for the rigidity could be found were studied before the introduction of modern histological methods In some cases it is possible that the symptoms depended on basal ganglia lesions which were overlooked or could not be demonstrated

Batten (104), whose exhaustive knowledge of the neurological affections of childhood enabled him to speak with authority, stated that cerebral diplegia is the result of four different pathological conditions, "atrophic sclerosis," arrested development of the brain, intra-

uterine occlusion of the cerebral vessels, and various types of meningitis. It is evident that he used the term diplegia to include all bilateral paralyses of cerebral origin. "Atrophic sclerosis," Batten believed, is the most frequent of all types of diplegia.

We must admit that it is possible for symmetrically placed lesions over the convexity near the midline to simulate the clinical picture of cerebral diplegia exactly. No doubt, bilateral meningeal hemorrhages may cause such a syndrome in rare cases, although the writer has been unable to find a report of any case of true congenital diplegia in which this lesion was found. Another possible cause of diplegia is thrombosis of the longitudinal sinus. Sir William Gowers stated that he believed some diplegias were due to sinus thrombosis, although he had no anatomical evidence to support the theory. In 1915, Holmes and Sargent (105) reported some cases of gunshot wounds of the vertex which involved the longitudinal sinus and produced a cerebral paraplegia with less severe involvement of the arms. Cushing (106) believes that it is the laceration of the cortex and not occlusion of the sinus which causes the paraplegia in such cases. More recently, Wilson (107) has published a case of paralysis of the legs resulting from syphilitic thrombosis of the longitudinal sinus in an adult. The writer has included in appendix C the case of a child in which thrombosis of the longitudinal sinus occurred at birth or very soon afterwards and resulted in general rigidity. Had this child lived it is possible that a picture similar to congenital diplegia might have developed. A similar case is also abstracted in which recovery without residual symptoms occurred. However, the anatomical evidence lends no support to the possibility that either meningeal hemorrhage or thrombosis of the longitudinal sinus is a frequent cause of congenital diplegia. A certain percentage of the bilateral congenital paralyses are due to porencephalic cavities in both hemispheres. Etiologically these cases are different from the true diplegias and it is often possible to distinguish them clinically, since lesions deep in the hemispheres produce bilateral hemiplegias and not true diplegias. It seems important to make the distinction between diplegias and double hemiplegias whenever it is possible to do so.

The pathological anatomical basis of congenital athetosis is described by the Vogts (108) under the term of "état marbré." In

this condition the lesion is restricted to the caudate nucleus and the putamen and consists in scattered areas in which nerve cells are absent and seem to be replaced by a fine network of medullated nerve fibers. In Weigert myelin stain preparations the stratum has a mottled appearance, hence the name. In a recent article the Vogts state that they now regard this condition as the result of a pre-natal process.

*Analysis of cases from the Harriet Lane Home for Children*

Two hundred and thirty-five cases of bilateral spastic paralysis are to be found in the records of the Harriet Lane Home. The writer has analysed 200 of these. These children were seen in the out-patient department, usually in early infancy. In many cases it was impossible to obtain an accurate history because of language difficulty or ignorance of the parents, but on the average the histories were full and usually contained negative as well as positive statements about birth and early infancy. Almost without exception these children suffered from severe malnutrition and the neurological condition was often completely overshadowed by their metabolic disturbances. Detailed neurological examination was often impossible because of illness or early age. Many of these children died while still under observation, although few were followed beyond a few weeks, and the majority probably failed to reach the second year. Under such circumstances it is impossible to differentiate this group with more than approximate accuracy, and, although it is certain that most of these cases are true diplegics and paraplegics, no doubt there are double hemiplegias included, and it is probable that a number of birth injuries are scattered through this group. A history of abnormal labor was obtained in only 15 per cent of cases. Convulsions at birth or in the first two weeks occurred in 16 per cent, and feeble respiration and nursing were noted in about 32 per cent. A history of prematurity was given in 33 per cent of cases. It is not wished to put too much stress on these figures because of their probable inaccuracy, but we will find in the analysis of the asymmetrical paralyses that a very much greater number of abnormalities of labor are reported. On examination, 71 or 35 per cent showed heads below normal size. Mental defect obviously could not be estimated accurately, but was almost invariably present. The most striking fact was the perfect bilateral

symmetry of the motor disturbance In only 5 cases out of 200 was there any preponderance of paralysis on one side This fact is hard to reconcile with the theory that such cases are due to birth injury, as we have found that in at least half the cases of hemorrhage over the convexity the extravasation is confined to one side, and when it is bilateral it is usually of unequal extent Hence, we would expect, if birth injury were the true cause, to find just as many hemiplegias as diplegias and unequal involvement of the two sides in the diplegias However, only seventeen congenital hemiplegias are to be found in the Harriet Lane records It seems probable that most of the 5 cases in which the motor disturbance was asymmetrical were true birth palsies However, the brain of one child with slightly unequal involvement of the two sides showed "atrophic sclerosis" at autopsy

Autopsies on 6 diplegics<sup>1</sup> were secured, none of which revealed any condition to be attributed to birth injury Two brains showed no gross abnormality Only one was examined microscopically and no degenerations were found These 2 cases, therefore, fall into the group described by Spiller Three more brains showed the gross appearance of "atrophic lobar sclerosis," and one which was examined microscopically showed the characteristic appearance of that condition The fifth brain was malformed, showing absence of the anterior corpus callosum, septum lucidum, fornix and falx

It is interesting that Sachs and Osler found hemiplegias more frequent than diplegias, although many times as many diplegics as hemiplegics are included in the Harriet Lane records It is probable that the tendency to nutritive disturbances and early death in the diplegic group may account for this discrepancy, as most of these children die before they reach the neurologist

In conclusion we may say that true congenital cerebral diplegia is apparently unrelated to birth injury or meningeal hemorrhage It depends on at least three anatomical conditions Perhaps the commonest pathological picture is the so-called "atrophic lobar sclerosis" as described by Collier, Freud and others The brains described by Spiller, Rhem, and Ganghofner which show slight defect in the pyramidal tracts undoubtedly constitute a distinct type of diplegia, which is

<sup>1</sup> A seventh necropsy has been secured recently Grossly the brain is normal Microscopic sections are not yet available

probably to be regarded as a defect of development. The simply convoluted brains which indicate disturbances in development in the early months of fetal life are another type. The athetotic cases, the Vogts have shown, are dependent on the condition known as "état marbré." It is probable that spastic diplegia may be simulated by gross lesions including birth injuries, but it does not seem probable from the material available that any considerable percentage of cases can be accounted for in that way. Cases of birth injury are probably always to be distinguished from true diplegia anatomically, and the differentiation can usually be made clinically.

#### CONGENITAL MONOPLEGIAS, HEMIPLEGIAS AND DOUBLE HEMIPLEGIAS

In 1889, Osler wrote as follows,

In infantile hemiplegia a great majority of the cases occur within the first three years of life, and in only a limited number is the condition congenital, either the result of intra-uterine disease or of accident during parturition. In bilateral hemiplegia and paraplegia the reverse holds good, in a large proportion of the cases the trouble dates from birth and is the result of injury to the child during its passage into the world.

Osler did not distinguish between double hemiplegias and diplegias, but his excellent description leaves no doubt that he was dealing with true diplegias.

Freud and Collier have taken a very different, almost exactly opposed, point of view. Collier concludes that monoplegia, hemiplegia, and even double hemiplegia may result from gross cerebral birth injury, but never true diplegia. He admits, however, that it may be impossible on clinical grounds to distinguish double hemiplegia from severe diplegia with general rigidity. The writer is entirely in sympathy with these views.

Batten believes that there are three pathological bases underlying congenital hemiplegias, unilateral arrest of development, intra-uterine occlusion of the cerebral vessels and birth injury to the cortex. The vascular lesions are the least frequent, he thinks. Unquestionably the great majority of infantile monoplegias and hemiplegias are acquired in the early years of life, as Osler states, but a considerable percentage of cases are congenital, and without doubt most of these



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are the result of birth trauma. Indeed, Osler found 9 among his 120 infantile hemiplegias in which he believed such an etiology was probable. The writer discovered 17 congenital hemiplegias and monoplegias in a total number of 45 in the Harriet Lane Home records. These case histories are given in brief in appendix C. In addition 8 congenital hemiplegias with focal convulsions were found in the records of the surgical department. In these cases operative notes are available. Brief abstracts are given in Appendix E. One case of congenital spastic paralysis of the leg is described in Appendix A. Eight cases of congenital spastic paralysis were found in a total of 200 cases of hydrocephalus. These are abstracted in Appendix D. The pathological anatomy was available in 10 cases in all. In 3 hemiplegias there was evidence of old organized subdural clot with atrophy and scarring of the cortex beneath. In 2 hemiplegias and 1 monoplegia there were found porencephalic cavities in the cortex. In 3 more hemiplegias there was local atrophy and scarring with thickening and cyst formation in the overlying pia-arachnoid. In 1 case of bilateral hemiplegia the periventricular type of porencephaly of Schwartz was found. In comparing these hemiplegias and monoplegias with the true diplegias the following facts seem significant. In these asymmetrical paralyses there is a history of abnormal labor in an extremely large (circa 70) percentage of all cases. The heads of these children are of normal size or even larger than normal, and sometimes asymmetrical. Intelligence is comparatively unaffected. The pathological findings are consistent with the diagnosis of birth injury.

Another group of cases may be considered with profit at this juncture. The condition known as "hemorrhagic pachymeningitis," or infantile subdural hematoma, presents an interesting analogy to the meningeal hemorrhage which occurs at birth. The extravasation in "pachymeningitis" is over the convexity and is often bilateral, in addition it is in some cases of traumatic origin. The clinical signs include papilledema with hemorrhages in the retina, enlargement of the head, vomiting, meningeal irritability and retraction of the head. There are usually no signs of focal cerebral lesions. The chief point of interest in the present discussion is that these children have large heads and not small ones, although most of these cases occur months after birth when the head does not enlarge so readily as in younger

infants If a child with "pacchymeningitis" survives the acute stage of the malady, recovery may be complete Rosenberg (109) reports that out of 14 patients he was able to trace after several years, 5 were dead of various illnesses, 2 were idiots, 1 an imbecile, 1 neurotic, 1 stuttered, 2 wet the bed and only 2 were quite normal However, none were paralytic and no syndrome in any way resembling cerebral diplegia resulted Only 1 of 6 cases observed by the writer showed any paralysis In this case paralysis of one arm was noted

From the material available the conclusion seems indicated that the congenital hemiplegias, monoplegias and the double hemiplegias, with large, normal or asymmetrical heads are in most cases to be considered true birth palsies Intra-uterine arrests of development and vascular occlusions undoubtedly constitute a part of this group, but probably a smaller part

#### VI RELATION OF CEREBRAL BIRTH INJURY TO HYDROCEPHALUS

It has been suggested by various authors from time to time that internal hydrocephalus might sometimes result from intracranial hemorrhage at birth No very definite pathological evidence has been brought to support this theory, but it is quite conceivable that the organization of blood in the ventricular system or in the subarachnoid spaces might cause enough obstruction to the circulation of the cerebrospinal fluid to produce hydrocephalus Siegmund and Crothers have mentioned hydrocephalus as one of the possible sequels of birth injury, and Ross (110) and Maclaure (111) have reported cases in which hydrocephalus developed in babies who had suffered birth injury Fraser and Dott believe that some types of hydrocephalus are related to intracranial hemorrhage at birth

#### CLINICAL DISCUSSION

Many congenital cases of hydrocephalus show little, or no enlargement of the head at birth Often nothing is noticed until the child is two or three months old, when it is discovered that the head is increasing in size at an abnormal rate Even at birth it is often possible to suspect hydrocephalus because of abnormally large fontanels, wide separation of the sutures, or thinness of the bones, especially when there is spina bifida or some other commonly associated malformation

In such cases the diagnosis can be made definitely by ventriculography. If the progress is rapid the head may grow at an astonishing rate and there may be lethargy, vomiting and even convulsions. If the progress is slow there are usually few signs or symptoms and the atrophy of the brain is often extreme when the enlargement of the head is only moderate. Spastic weakness of the extremities and defective mental development are almost invariably present, but much less severe than one would expect from the reduction of brain tissue. Typically the optic nerves are pale and sharply defined, but there may be papilledema. Vision is generally somewhat reduced, and sometimes lost. Death may occur in a few months, or more rarely the process may become arrested and the patient may survive for years with a large head and more or less mental defect. Infrequently the head is much enlarged at birth so that delivery is difficult or impossible. Some of the cases of so-called "external hydrocephalus" are believed to be cases of internal hydrocephalus which have run their course in utero with collapse of the cortex. These cases reveal at section nothing but the basal ganglia and brain stem in a cranium full of clear fluid.

The hydrocephalus which so commonly follows meningitis usually develops more slowly than the congenital variety. After the cranial sutures unite firmly, which occurs at some time between the sixth and ninth month, enlargement of the head is much slower and no longer gives any information about the degree of cerebral reduction. After the fontanels are completely closed, which should occur before the second year, enlargement of the head is infrequent but may occur up to ten years in exceptional circumstances.

#### THE CIRCULATION OF THE CEREBROSPINAL FLUID

Much of our present knowledge of this subject is due to the fundamental work of Weed and Dandy. These authors have demonstrated that the cerebrospinal fluid is secreted almost entirely by the choroid plexus of the cerebral ventricles with the probability that a small part may originate from the perivascular spaces of the cortical vessels. This fluid formed in the lateral ventricles flows through the foramen of Monro into the third ventricle, through the aqueduct of Sylvius into the fourth ventricle and through the foramina of Luschka and the

median foramen of Magendie into the cisterna magna. From the cisterna the cerebrospinal fluid passes anteriorly under the base and then up over the convexity in the sulci between the cerebral convolutions where it is absorbed into the dural sinuses through the arachnoidal villi. After leaving the fourth ventricle the cerebrospinal fluid is confined entirely to the subarachnoid spaces.

#### PATHOLOGICAL ANATOMY OF INTERNAL HYDROCEPHALUS

No real understanding of this difficult subject existed prior to 1913, when the first of Dandy's brilliant contributions appeared, although a great deal of important but ill-correlated information had existed for many years. Even yet some authors fail to grasp the basic principles involved. Dandy has shown that almost all cases of hydrocephalus are due to obstruction at some point in the cerebrospinal fluid pathways. In some cases the obstruction is in the iter, in others at the foramina of exit of the fourth ventricle, and in a third type the block is in the cisterna at the base of the brain. The first two types are designated clinically as "non-communicating" hydrocephalus, because dye injected into the ventricles is not recovered in the spinal fluid on lumbar puncture. The third type is termed "communicating" hydrocephalus because the dye injected into the ventricles can be found in a few minutes in the lumbar cul-de-sac. Spiller (115) has described a case of unilateral hydrocephalus resulting from cicatricial stenosis of the foramen of Monro.

Cases have been reported in which an increased production of cerebrospinal fluid seemed to be the cause of hydrocephalus. Thrombosis of the vein of Galen has been found and "hypertrophy of the choroid plexus" is another unusual finding. These conditions are excessively rare and are mentioned merely for the sake of completeness.

When the iter is occluded, examination of the cut surface of the midbrain shows no trace of a canal. Microscopically a few strands of ependymal epithelium can be found in most cases, sometimes in the form of a flattened tube. There may be several small channels and sometimes minute cysts lined with epithelium are found. Spiller was the first to give a good microscopic description of this condition. Schlafli and Gere (116) have reported the anatomical findings in 8 cases of hydrocephalus with closure of the iter. Three cases showed

small tumors, 2 cases showed inflammatory lesions, one of which was syphilitic, and 3 showed the condition previously described by Spiller Guthrie found 8 cases in which occlusion of the iter followed meningitis. One of Dandy's cases showed a thin transparent diaphragm stretching across the aqueduct.

The author has examined the midbrain microscopically in 11 cases of hydrocephalus in which the iter was occluded. In 5 cases the condition was congenital as shown by the history and presence of other congenital malformations. In these, several small channels lined with epithelium were found, but none of them seemed to be continuous (fig. 1). One got the impression that the iter had never been properly formed in these cases. In 2 cases with a history of meningitis an entirely different picture was seen. Here the outlines of an aqueduct of normal size could be made out distinctly, but the lumen was occupied by a fibrous mass of glial tissue. Many small spaces lined by ependymal cells were to be seen around the margins of this plug. These represented the original ependymal lining of the iter. In 1 case the signs of an active inflammatory process were still present (fig. 2). In 2 more cases, which will be discussed more fully later, there was a history of birth injury. In these cases exactly the same plugging of the aqueduct was found as in the post-meningitic cases (fig. 3). Thus it seems possible to distinguish clearly between the congenital cases in which the aqueduct has been imperfectly formed and those in which an iter of normal size has been plugged up by some post-natal process.

Dandy describes two different conditions found at operation and autopsy in cases of obstruction of the foramina of the fourth ventricle. In one the fourth ventricle is represented by a greatly dilated cyst with a thin, transparent wall. The vermis is lacking and the cerebellar hemispheres are small and displaced downwards. There are no adhesions and no other signs of a previous meningitis. He believes this is a congenital defect of development, and refers to the work of Blake (118) and Heuser (119) who have shown that the foramina of the fourth ventricle develop by a gradual thinning of the ventricle wall during early embryonic life. In most cases, however, he finds dense adhesions and thickening of the meninges, obviously the result of meningitis. The same condition may be found in congenital cases as in those which follow meningitis in infancy.

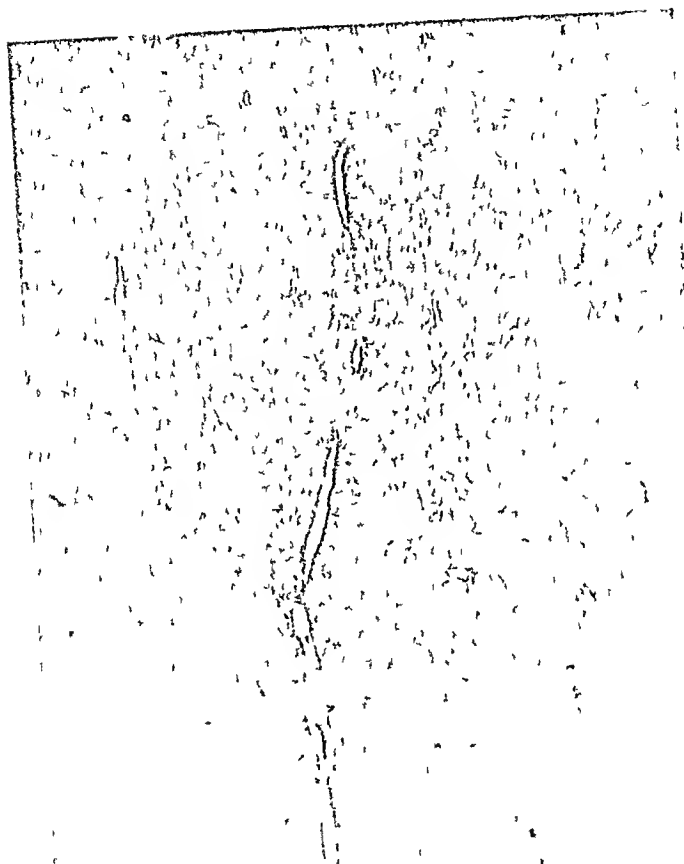


FIG. 1. SECTION OF CONGENITALLY MALFORMED AQUEDUCT SHOWING MULTIPLE INTER-  
DUCTIONS OF NARROW SPLIT



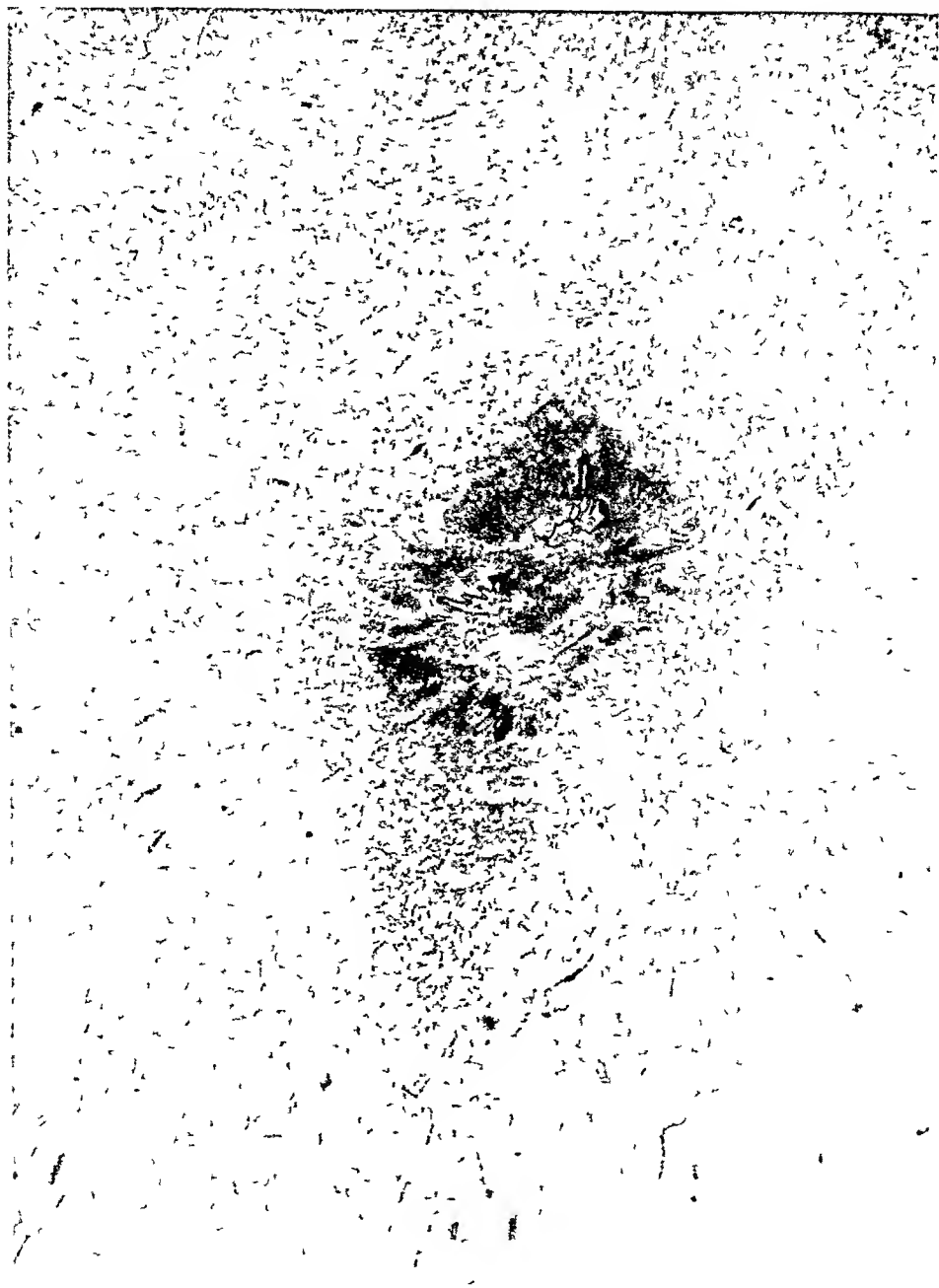


FIG 2 SECTION OF WELL FORMED AQUEDUCT "PLUGGED" BY ORGANIZATION OF INFLAMMATORY EXUDATE IN COURSE OF MENINGITIS  
Evidences of inflammatory process still present

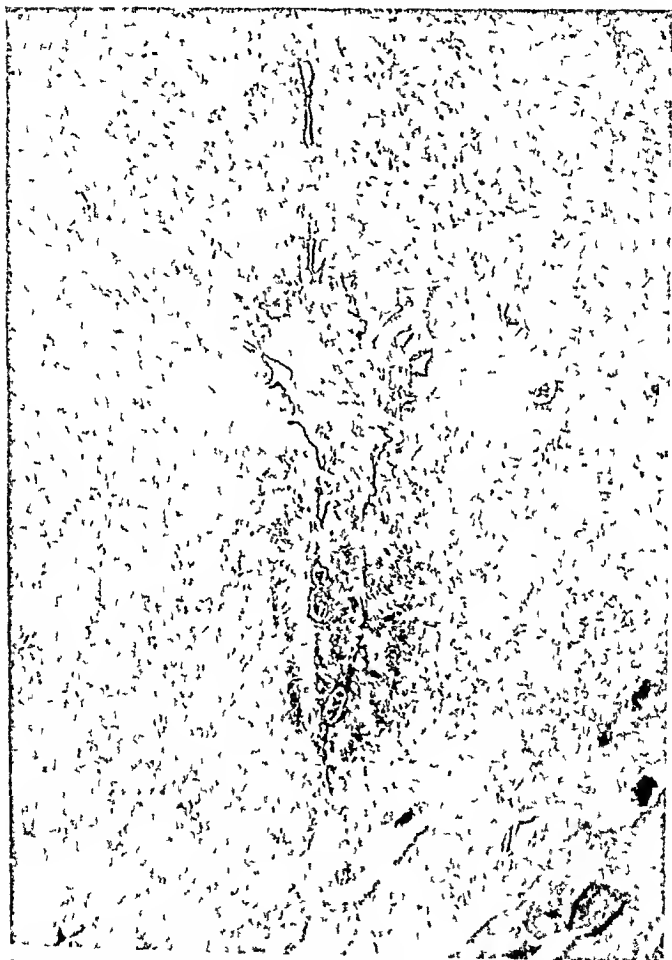


FIG 3 SECTION OF WELL FORMED AQUEDUCT "PLUGGED" WITH FIBROUS TISSUE PROBABLY DUE TO ORGANIZATION OF AN OLD INTRAVENTRICULAR HEMORRHAGE AT BIRTH

In the communicating type, when the obstruction is at the base, there is in most cases evidence of old meningitis. Fraser and Dott have also invariably found adhesions at the base in this form of hydrocephalus which until Dandy's publications was called "idiopathic" hydrocephalus. Dandy also describes two cases of communicating hydrocephalus in which no signs of previous meningitis were found. He believes that these cases may be caused by a failure of the subarachnoid channels under the base to develop. Weed has shown that the subarachnoid spaces develop in pig embryos by a splitting of the periencephalic mesenchyme and begin to appear soon after the foramina have opened.

#### THE ETIOLOGY OF INTERNAL HYDROCEPHALUS

Dandy believes that, if we exclude the post-natal cases which are due to meningitis, hydrocephalus is always congenital. The fact that the head is of normal, or nearly normal, size at birth is not evidence against a congenital origin, because Dandy has been able to demonstrate by means of ventriculography that the brain is often greatly reduced at birth, although the head does not become noticeably enlarged until several months have passed. It is probable that the intra-uterine pressure has some effect in preventing the enlargement of the skull before birth. A small percentage of congenital cases, Dandy believes, are due to the failure of the foramina of the fourth ventricle or of the subarachnoid channels to develop. The vast majority are due to intra-uterine meningitis which may seal up the iter, the foramina of the fourth ventricle or obliterate the cisterna at the base. The evidence for this theory is that at operation, or autopsy, dense adhesions are found in the posterior fossa and under the base exactly like the adhesions which follow meningococcus meningitis in extra-uterine life. He has never been able to obtain any history of maternal illness which would give any explanation for this condition.

Fraser and Dott believe that intracranial hemorrhage is an important etiological factor which has been overlooked. "We possess very definite evidence that an intracranial hemorrhage produced at birth is liable to be followed by a hydrocephalus if the location of the hemorrhage is subtentorial in its distribution. These remarks apply only to ventricular (i e., non-communicating) hydrocephalus." They ob-

tained a history of difficult delivery in 7 of their 21 cases and "subsequent operative interference revealed the presence of a hemorrhagic effusion in the membranes at the base of the brain" These conclusions are less convincing because the authors do not recognize congenital hydrocephalus unless there is spina bifida or the head is "considerably enlarged at birth, so much so, sometimes, as to constitute an obstruction to delivery" They admit, "In certain cases (without spina bifida) the statement was offered that the parents noticed the head to be somewhat enlarged at birth, but it is doubtful if any real weight can be attached to this observation" However, they have confirmed Dandy's statement that hydrocephalus may be demonstrated by ventriculography at birth in babies with heads of normal size

On the basis of extensive pathological experience, Guthrie believes that post-natal cases of hydrocephalus are the result of meningitis and congenital cases are due to defects of development or intra-uterine meningitis

To determine whether birth injury has any importance in the causation of hydrocephalus, the writer has analyzed 100 autopsies of hydrocephalics (see Appendix D) In 11 cases there was evidence suggestive of intracranial birth hemorrhage, but 4 cases were at once excluded because there was definite proof that the hydrocephalus had existed at birth In 2 other cases the head enlarged so rapidly after birth that it seems most probable that the condition was congenital In 5 cases, however, it seems possible that the hydrocephalus may have been more closely connected with the intracranial hemorrhage Two of these showed symptoms suggestive of birth injury in the first few days They both had hemiplegia and later developed focal convulsions Both had great reduction of the brain without enlargement of the skull At autopsy both showed evidences of old subdural hemorrhage and destruction of the cortex with "plugging" of the aqueduct It does not seem possible, however, to exclude with certainty an early inflammatory lesion A third case was associated with hemorrhagic disease of the new-born and the ventricles were found to be small by ventricular puncture on the seventh day Repeated hemorrhages occurred and the brain was greatly reduced at autopsy, but the skull was only moderately enlarged The aqueduct was full of blood clot



carried into the aqueduct by the circulation of the cerebro-spinal fluid and remain long enough to give rise to an organized "plug"

In conclusion it seems evident that birth injury can not be more than an exceptional cause of chronic hydrocephalus. The extravasation of blood into the ventricular system or subarachnoid spaces of infants produces an increase in intracranial pressure, enlargement of the head, dilatation of the ventricles and a mild inflammatory process in the meninges. In the vast majority of cases such symptoms are transient and disappear when the blood is absorbed. It is possible that the aqueduct of Sylvius may be plugged by a blood clot or bits of necrotic brain tissue which becomes organized and a progressive hydrocephalus ensues. In six cases out of two hundred it is probable, but not certain, that this actually took place. Most of these cases were easily distinguished from the common type of chronic hydrocephalus. Almost all cases in which internal hydrocephalus and intracranial birth hemorrhage coexist are found to be cases of congenital hydrocephalus whose thin skulls and large heads have predisposed them to birth injury. It seems probable that some of the cases of arrested or non-progressive hydrocephalus associated with congenital hemiplegias and other spastic paralyses are to be attributed to intracranial injury at the time of birth.

## VII RELATION OF EPILEPSY TO CEREBRAL BIRTH INJURY

### "ESSENTIAL" EPILEPSY

By definition "essential" epilepsy bears no demonstrable relation to brain disease or injury, but occurs in otherwise healthy people without obvious cause. Clinically, however, the term is loosely used to apply to epilepsies without signs of focal brain lesion. It is well known that a certain percentage of such patients show gross brain lesions at necropsy. Southard (120) and Thom found only 68 grossly normal brains out of a total of 205 brains of epileptics. It is obviously difficult to obtain any figures of the incidence of birth injuries in such a clinical group because as soon as such an injury becomes probable the case is placed in another group. However, the recent studies of Patrick and Levy (121) throw some light on this problem. They compared the histories of 500 "ideopathic" epileptics with those of

750 unselected normal children. In only 5 of the epileptic cases was abnormal labor the "assigned" cause. The incidence of forceps delivery and asphyxia were about the same in both groups. In the epileptic group 3.6 per cent were delivered by forceps and 2.4 per cent were asphyxiated at birth. It must be borne in mind that these figures apply only to "essential" epilepsy in the clinical sense.

The anatomical changes found in "essential" epilepsy fall into three groups. First, developmental anomalies including various heterotopias and malformations of the cortical architecture. These findings have been stressed recently by Pollack (122) and by Geitlin (123). Secondly, acute changes in the nerve cells and fibers found in brains of patients dying in status epilepticus. Pierce Clark and Prout (124) gave a good description of these in 1903, and Bevan Lewis (125) demonstrated similar changes as early as 1890. Kogerer (126) has discussed the same problem recently. The third group includes the chronic changes such as degeneration and disappearance of the cortical cells, subpial gliosis and sclerosis of the cornu ammonis. Spielmeier (127) has given an exhaustive description of these lesions. Meyer (128) has shown, however, that the last two groups of changes are merely secondary and not to be considered in any sense characteristic. There is, therefore, no clinical or anatomical evidence to connect birth injury in any way with "essential" epilepsy.

#### "SECONDARY" EPILEPSY

The relation of recurrent convulsions to brain injuries of various types is established beyond any doubt. Fracture of the skull, gunshot wounds of the brain (129), cerebral neoplasms (130), granulomas, abscesses, scars of old inflammatory or vascular lesions, all are apt to result in convulsions, general or focal. Dandy (131) has found local areas of cortical atrophy and scarring at operation in a very large percentage of all cases of epilepsy. He has also been able to demonstrate these lesions by ventriculography since, as he shows, any loss of substance in the brain is compensated for by an out-pouching of the ventricle and an enlargement of the subarachnoid space. S. A. K. Wilson (132) has recently published a critical analysis of the relation of trauma to diseases of the nervous system. He writes as follows: "It has been asserted almost universally that trauma may cause

epilepsy, I have never been able to understand why I associate myself entirely with Turner when he insists that 'it is difficult to avoid the conclusion that something more than local tissue alterations is requisite for the production of the seizures of traumatic epilepsy, and the determining agent, in my opinion, is an inherited or inborn constitutional predisposition to nervous instability and epilepsy' R G Gordon has obtained evidence of a neuropathic predisposition in 75 per cent of his cases, in a series of my own, from the pensioners' clinic at the National Hospital, Queen Square, I have found similar evidence in 80 per cent " Obviously something more than the brain injury is necessary for the production of epilepsy because the vast majority of patients with cerebral lesions do not have convulsions, yet no one that deals with neurological patients and observes the frequent instances in which focal convulsions follow injuries to the brain can help feeling that brain injury is at least one factor in the production of epilepsy It might be permissible to point out that "nervous instability" and "neuropathic predisposition" are rather illdefined hereditary factors which most of us share with the epileptics

In children, it is usually taught, brain injuries are even more likely to lead to epilepsy than in adults Holt and Howland state that epilepsy occurs in from 33 to 50 per cent of all infantile cerebral palsies Osler found 35 cases of epilepsy out of 120 infantile hemiplegias Spratling states that 40 per cent of all infantile hemiplegias develop epilepsy Five of the 17 cases of congenital hemiplegia from the Harriet Lane Home are subject to convulsions, and there is no doubt that about one third of all children with spastic paralysis due to birth injury develop focal, or less frequently general convulsions Eight cases of focal epilepsy associated with congenital hemiplegias and monoplegias were found in the records of the surgical department These cases are abstracted in Appendix E

Spratling claims that 11 per cent of 1070 cases of epilepsy are to be attributed to infantile cerebral palsies About one-third of these, he thinks, are congenital In order to gain some idea of the frequency of "secondary" epilepsy following cerebral birth injury, the writer analyzed the histories of 100 unselected cases of epilepsy seen in the neurological out-patient department In only two cases was there a history of birth palsy to be obtained, although there was a large percentage of



focal epilepsies in the group. However, it was felt that this result was inconclusive because many of the histories were meagre and probably inaccurate. Many of the patients were adults and had forgotten anything they might have been told about their birth.

Another series of 100 unselected case histories of epileptics from the Harriet Lane Home records was analyzed. Nine of these cases were of the focal, or Jacksonian, type and 3 of these were definitely associated with birth injury. Two of these 3 patients had congenital hemiplegias and the third had sustained an injury to the left side of the head at birth and later developed focal attacks on the right side. Five congenital diplegics were found in this group and 6 post-natal hemiplegias. In all 14 cases were associated with spastic paralyses. It is evident that these figures are in essential agreement with those of Spratling, and it seems probable that approximately 2 or 3 per cent of all epilepsies are related to birth injury.

#### VIII RELATION OF CEREBRAL BIRTH INJURY TO MENTAL DEFECT

Imperfect mental development, or amentia, occurs in many different conditions, few of which are related in any way to abnormalities of labor. The overwhelming majority of such cases are due to congenital defects of various types. A common one is the "mongolian" idiot. The microcephalic with the simply convoluted brain is frequently encountered. Many microcephalics are also diplegic and have already been discussed. In cases of so-called simple amentia the brain may be grossly normal, but on microscopic examination a deficiency of cortical cells or an abnormal cortical architecture are revealed. Tuberosc sclerosis is a rare type of congenital abnormality of the nervous system associated with multiple tumor formation and amentia. The "hypertrophic" brain is also a rare condition found in idiots with large heads. Such brains are of great size and weight and show extreme complexity of the convolutions. Scaphocephaly, oxycephaly and acrobradycephaly are all congenital malformations of the skull sometimes associated with mental defect. The most important factor in all these types of congenital defects of cerebral development, Mott believes, is a defective germ plasm. Tredgold and Goddard hold similar views.

Another group of conditions results in inhibition of mental develop-

ment soon after birth. Prominent among these is thyroid deficiency. Various types of infantile encephalitis, juvenile general paresis, and several forms of infantile cerebral degenerations belong in this group. Idiots by deprivation of sense organs, deaf-mutes, etc., may be related to early meningitis. Early epilepsies may also be included.

Only three types of mental defect have any possible relation to birth injury—the spastic, the hydrocephalic and the epileptic, all of which have been discussed already. There remains the remote possibility that some birth injuries might involve large areas of cortex without producing paralysis or epilepsy. Such cases must obviously be excessively rare.

Potts (134) has stated that 12 per cent of 5430 cases of mental defect are to be attributed to birth injuries. He apparently compiled these figures from the literature and gives no references. Beach and Shuttleworth (135) estimate that 17.5 per cent of idiots are the result of birth injuries. It is evident that these figures are excessive and it is probable that both authors have included the diplegias among the results of birth injury. Tredgold and Bolton (136), on the basis of an extensive pathological experience, both feel that mental defect of any pronounced degree is rarely related to birth injury. Tredgold states that not more than 1.5 per cent of all idiots can be traced to birth injury, and these are invariably epileptic.

## IX. CONCLUSIONS

It is not possible to reach any final conclusions about the exact limits of the group of cerebral birth palsies from the evidence available. The cases of spastic paralysis have been difficult to analyse, and in many cases a satisfactory neurological examination has not been possible. Very few cases of intracranial hemorrhage which survived could be found and these have not been followed long enough. The pathological anatomy is very meager and usually imperfectly described and studied. Before any clear understanding of these problems can be secured a large series of detailed pathological-anatomical studies must be made with adequate clinical control. However, unsatisfactory as the material may be, certain impressions have been gained in the course of this investigation which it seems permissible to state in the form of tentative conclusions.

First, very convincing evidence has been gathered that the congenital diplegias which constitute by far the largest group of infantile spastic palsies as seen in the pediatrics department (235 out of 280 in all) are not to be attributed to meningeal hemorrhage at birth, but are the result of various pathological processes of intra-uterine origin. Four principle arguments support this conclusion. Meningeal hemorrhage is in at least half the cases unilateral, and when bilateral is almost always unequal on the two sides, cerebral diplegias are, with very few exceptions, bilaterally symmetrical. The heads of diplegics are usually either definitely microcephalic or slightly below normal size, meningeal hemorrhage causes rapid enlargement of the head. Children who are known to have intracranial bleeding at birth or in infancy do not develop cerebral diplegia. Lastly, the pathological anatomy of true congenital diplegia is such that it can not be reconciled with any theory of birth injury.

If the above statements are correct it will be seen that cerebral birth injuries are rare rather than common, and the great mass of infantile palsies can no longer be lightly attributed to faulty obstetrical procedures.

No final statement can be made about the relation of intracranial birth injury and chronic hydrocephalus. Undoubtedly, marked enlargement of the head may occur with extensive bleeding into the ventricular system or subarachnoid spaces, but in most cases the blood is eventually absorbed without leaving any permanent obstruction to the circulation of cerebrospinal fluid. Possibly in some cases chronic hydrocephalus may result from plugging of the aqueduct by a blood clot or a bit of necrotic brain tissue, and organization of the obstruction. It seems likely that some children with large heads and congenital asymmetrical spastic paralyses owe their condition to birth injury. Intracranial hemorrhage is not uncommonly an accidental complication of congenital hydrocephalus because these infants have large heads and thin skulls.

The common diffuse meningeal hemorrhage which is not large enough to cause death apparently leaves no residuum in the overwhelming majority of cases. The real birth injuries to the brain are caused by the rarer intracerebral hemorrhages and necroses, by depressed fractures with laceration of the brain, and undoubtedly, by

some more or less encapsulated meningeal hematomas which compress and soften the cortex. All the evidence which the writer has been able to collect seems to indicate that the true cerebral birth palsies are represented by the congenital hemiplegias, the monoplegias and the asymmetrical and unequal bilateral spastic paralyses. These children have large or normal heads, even in some cases asymmetrical heads. Their intelligence is on the average much greater than that of the diplegics. A history of birth injury may be obtained in a very large percentage of such cases and the pathological anatomy is quite consistent with the hypothesis of gross birth injury. Of course, it is realized that asymmetrical congenital defects of the brain are included with these cases and are probably clinically indistinguishable from them. Numerically this group, which the writer believes is principally composed of true cerebral birth palsies, is surprisingly small, just 17 out of 280 infantile cerebral palsies in the Harriet Lane Home records, if we exclude the 5 asymmetrical diplegias. These figures would mean that about 6 per cent of all infantile cerebral palsies are due to birth injury, but the group is not well enough defined to attempt any numerical estimation. Recurrent convulsions occur in about one-third or more of these cases, and we have already concluded that about 2 or 3 per cent of all epilepsies seen in children are related to birth injury. Severe grades of mental defect are probably not related to birth injury with the exception of that type which develops in association with frequent convulsions. Tredgold estimates that not over 15 per cent of demented patients who die in asylums owe their condition to birth injury and it seems probable that these figures are very approximately correct.

I wish to thank Dr. Adolf Meyer under whose supervision this work was carried out, and Dr. John Howland, Dr. Walter E. Dandy and Dr. J. Whitridge Williams for their criticism and permission to use their case histories.

## APPENDIX

### A. FOUR CASES OF INTRACRANIAL BIRTH HEMORRHAGE FROM THE OBSTETRICAL DEPARTMENT

There were approximately 50 cases in this series in which the diagnosis of intracranial birth hemorrhage was made or suspected. Out of the whole

group only 7 survived. In 3 cases lumbar puncture was not performed, and as no signs of an intracranial injury appeared later, these cases have been omitted. The remaining 4 cases are abstracted below.

*Case 1 (Disp H 38370, Obs. 10856)*

M C, first pregnancy, mother had seven convulsions, labor terminated by manual dilatation and high forceps, cut by forceps over left eye and left occiput, extraction difficult, deep asphyxia, did not cry for two hours, convulsions on second day, fontanel full, severe brachial plexus palsy on the left which improved gradually, at the age of several months mother noted child did not use right leg well, right arm also slightly clumsy, eyes always crossed, no more convulsions, mental development retarded, never learned to talk well

P E. At age of five years head 51 cm in circumference, residuum of old upper arm brachial plexus palsy on the left, right leg very spastic and shows shortening and equinus position, left leg is used well, right arm is very slightly clumsy, eye movements are non-comitant, patient holds head to right as if there were right hemianopia, can say only a few words, but is good natured and obedient.

*Case 2 (Obs. 10694, Ped. 26279)*

L B, colored, first child, delivered by mid forceps after manual dilatation, blades slipped and head was cut, deep asphyxia, resuscitated with difficulty, on second day fontanel bulged, marked rigidity, on third day spinal fluid showed much altered blood, rapid improvement and on discharge on sixteenth day seemed well

P. E. At the age of two years head normal size, no weakness or paralysis well nourished and mental condition seemed normal, moderate rickets.

*Case 3 (Ped 40512)*

A G., child of healthy parents, born at term by difficult labor, episiotomy was necessary, moderate cyanosis but seemed normal, on second day grew rigid and had many convulsions, spinal fluid full of slightly altered blood, jaundice, spinal fluid cleared up gradually in three weeks, three lumbar punctures done in all, on discharge at three weeks child seemed well.

P E At five months head 42 cm, well nourished and development seemed normal At one year and nine months head 44.5 cm, no sign of spastic weakness, normal healthy child.

*Case 4 (Obs 15318)*

Baby W, first child, premature rupture of membranes, perineal dystocia, low forceps, strong traction required, episiotomy necessary, moderate asphyxia, abrasion over each ear, on the second day rigid, restless, frequent general convulsions, fontanelts tense, almost pure blood obtained from the cistern, on the third day fluid still bloody, rapid improvement, at thirteen days fluid almost clear, only slight rigidity

P E At five months normal healthy child, no rigidity or weakness

B ANALYSIS OF 200 CASES OF CONGENITAL BILATERAL SPASTIC PARALYSIS,  
MOSTLY CONGENITAL DIPLEGIAS (FROM THE HARRIET  
LANE HOME RECORDS)

## CONGENITAL CEREBRAL DIPLEGIA

*Case 1 (Ped 7040, Path 5127)*

M L McH, third child of healthy parents, one sibling living and well, second pregnancy resulted in four months miscarriage

P I The patient was born prematurely at about seven months, labor was easy and no instruments were necessary, weight was 5 pounds, there was some asphyxia and the child nursed very poorly

P E At seven days it was noted that the child was inert and signs of prematurity were evident. When seen again at three months there was some rigidity of the extremities, and a tendency to hold the legs crossed, the child swallowed with difficulty and was much undernourished. At eight months the head was 42 cm in circumference. When child was handled there was intense muscular rigidity and opisthotonos, when undisturbed apparently no muscular spasm, when objects were placed in the child's hands they were grasped and held until they were removed, the optic nerve heads were normal, the tendon reflexes were increased. At three years the child could not talk but made grunting sounds and could express its wants by this method, it swallowed with difficulty, the head was held up but the child could not stand or walk without support, there was intense general spasticity and "scissors gait," tendon reflexes were increased, mental development seemed much retarded,—patient seemed to recognize parents, however

Operation The meninges were thought to be thickened and an excess of fluid in the subarachnoid space was found. Nothing more than an exploration was attempted. The child died soon afterwards

Pathological anatomy The brain and meninges seemed normal, the

vessels were normal, no adhesions were seen, the ventricles were not dilated, the convolutions were smooth and full, the sulci not widened. Microscopically the pyramidal tracts in the cord showed no degeneration, it seemed possible that there may have been fewer fibers than normal but one could not be sure of this, however, the fibers did seem somewhat finer and of irregular size as compared with the posterior column fibers. Sections of the paracentral lobule showed no degeneration or gliosis but large pyramidal cells were possibly diminished in number, and giant cells were not easy to find. Sections through the basal nuclei showed nothing abnormal. All the cell studies were difficult because the material stained poorly. The brain weighed 1250 G.

*Case 2 (Ped 33486, Path 7978)*

M. D., second child of healthy parents, the first child died in infancy from unknown cause.

P. I. Birth spontaneous at term, weight 7 pounds, did not cry, respiration very irregular, cyanotic at times, did not nurse.

P. E. When seen at three days head was 36.5 cm in circumference, the fontanelles were full but not bulging, there was general rigidity and frequent convulsions, respirations were irregular and gasping, the child could not nurse, after several days it was discharged improved. At seven months the head was 38 cm, respiration was now normal, but there was marked general rigidity, no mental development had occurred and there were frequent convulsions. Spinal fluid was normal. At nineteen months the head was 39.5 cm in circumference, general rigidity and adductor spasm, marked under-nutrition, bronchopneumonia, death.

Pathological anatomy. The meninges were not thickened, the dural sinuses were patent, grossly there was some shrinking of the convolutions of the frontal lobes, the sulci in these regions were widened and possibly more numerous than normal, the shrinking seemed more marked at the foot of the gyri than at the apex, so some of the convolutions seemed undermined behind the central convolutions the cortex was grossly normal, the lateral ventricles were somewhat dilated, i. e., hydrocephalus ex vacuo.

Microscopic examination showed marked loss of nerve cells in the cortex of the frontal lobes and motor area and a secondary gliosis, there was no sign of an inflammatory process, in the spinal cord the pyramidal tracts were severely degenerated and there was also degeneration in the region of the uncrossed motor fibers and the direct and indirect cerebellar pathways (i. e., tracts of Gowers and Flechsig). The basal nuclei seemed normal.

*Case 3 (Ped 11112, Path 4747)*

T H, first child of healthy parents, born by long labor, no forceps, jaundiced ten days, very ill, at five weeks was noted to be stiff

TABLE 1  
*Analysis of 200 cases of congenital bilateral spastic paralysis*

	NUMBER	PER CENT
<i>Birth history</i>		
Convulsions in first two weeks	31	16 0
Feeble nursing and respiration	64	32 0
Difficult labor	30	15 0
Precipitate delivery	10	5 0
Prematurity	66	33 0
<i>Heads</i>		
Microcephaly*	71	35 5
Oxycephaly	3	1 5
Scaphocephaly	1	0 5
Asymmetrical heads	3	1 5
<i>Paralysis</i>		
Paraplegias	12	6 0
Spastic diplegias†	168	84 0
Asymmetrical bilateral paralyses†	5	2 5
Athetotic diplegias	12	6 0
Choreic diplegias	1	0 5
Flaccid diplegias	2	1 0
<i>Epilepsy</i>		
Convulsions, generalized	56	28 0
<i>Pathological anatomy</i>		
"Atrophic sclerosis"	3	
Gross malformation	1	
Grossly normal, defect in cortical cells (?)	2	
	6†	

\* This term should be qualified by the statement that the heads were usually only slightly under normal size and the children's general development almost always under par

† It is possible that there are some bilateral hemiplegias in this group

‡ Abstracted in appendix B

P E At four and one-half months poorly nourished, head 35 cm in circumference, internal squint, all tendon reflexes increased, cannot sit up or hold up his head, general spastic rigidity, spinal fluid negative, death of malnutrition and furunculosis

Pathological anatomy Brain showed full round convolutions, meninges



delicate, sulci not widened, no abnormalities of the vessels, ventricles not enlarged, microscopic examination not made, brain cannot be found for further examination

*Case 4 (Ped. 41534, Path 8207)*

W. J. Z , birth by easy spontaneous labor, no evidences of birth injury, nursed well and seemed normal until four months when it was noted that child did not hold up head normally, never could sit up, no signs of mental development, convulsions at six months, diarrhea and digestive disturbance developed

P. E. At six months head 35.5 cm in circumference, and somewhat pointed at top, weakness of all extremities, tendon reflexes increased, very little spasticity, no signs of mental development, marked under-nutrition, and death from pneumonia and otitis media

Pathological anatomy: Brain of normal size, falx and longitudinal sinus extend anteriorly only to fissure of Rolando, septum lucidum, anterior part of corpus callosum and fornix are lacking, anterior to the falx the convolutions interlock but do not fuse, rest of the brain shows no gross abnormalities, no microscopic examination made

*Case 5 (Ped 404445, Path 8059)*

W. H , born by easy, spontaneous labor at term, three sibs normal, mothers' first pregnancy was an eighth month miscarriage, patient had severe jaundice and many convulsions on the third day, very ill, never considered a normal baby, never learned to hold up head, or use arms or legs well, left arm was used a little better than the right, numerous "rigid spells" probably convulsions, no mental development

P. E At fourteen months head 48.5 cm in circumference, somewhat flattened in biparietal diameter and increased anteroposteriorly, left side of forehead is less prominent than the right, marked adductor spasm and spasticity of both legs, arms are relatively spared, but there is some motor disturbance in both arms, more severe on the right, tendon reflexes increased, bilateral extensor response, no signs of mental development, death a few days later from otitis media and pneumonia

Pathological anatomy: Gross atrophy of both frontal lobes, more severe on the left side, other lobes of brain are apparently normal and show full round convolutions, meninges delicate and vessels normal, gross appearance like that of brain in case 2 No microscopic examination made, brain cannot be found

*Case 6 (Pcd 39402, Path 8302)*

P T, full term, normal delivery, duration six hours, no forceps, deeply asphyxiated, three hours before child could be resuscitated, weight seven and one-half pounds, convulsions after breathing started

P E At two days head 36 cm, no superficial injuries, slight cyanosis, general rigidity noted, tendon reflexes increased, swallowing difficult, regurgitation through nose, fed by gavage, vomited, thought to have intracranial hemorrhage but cistern puncture gave normal fluid, convulsions ceased at six days At five weeks head 38 cm, nutrition poor At seven months head 43 cm, severe nutritive disturbance, furuncles, otitis media, pneumonia, death Never showed any signs of mental development always definitely rigid but neurological condition was overshadowed by metabolic disturbance

Pathological anatomy Brain small, weight 690 grams, atrophy of convolutions over whole surface but especially those on either side of the Sylvian fissure, brain abnormally hard, meninges normal, vessels normal, wasting perfectly symmetrical, spinal cord not examined, no signs of hemorrhage, no microscopic examination Brain cannot be found

## ASYMMETRICAL AND UNEQUAL BILATERAL CONGENITAL SPASTIC PARALYSES

*Case 7 (Pcd 27744)*

E L B, born at term by long difficult labor, forceps required, deep cyanosis, difficult resuscitation, very limp and weak for a week, did not nurse Face asymmetrical, drawn to the right, no convulsions, left arm and leg were never moved freely, gradual improvement, has always seemed bright

P E At ten months head normal size, child seems normally alert, left arm very spastic, right arm used well, some motor disturbances in both legs, more marked on the left, back and neck also weak

*Case 8 (Pcd 36233)*

V M C, first child, born at eight months by difficult forceps delivery through contracted pelvis—said to have been injured but exact details are not available,—difficulty in using extremities noted in first few months

P E At three years head normal, right arm very spastic, both legs show some spasticity but this is more marked on the right, some tendency to internal strabismus, mental development seems normal

*Case 9 (Ped. 16611)*

W. H , second pregnancy, first was a miscarriage, born at term by difficult breech delivery, no signs of injury noted. At three months it was noted that child did not use left arm and leg as well as the right, late in holding up head

P. E. At two years head 50 cm in circumference, seems normally intelligent, left arm spastic, some spasticity and adductor spasm in the legs not stated to be unequal.

*Case 10 (Ped. 20710)*

W. P. W , third pregnancy, first two were miscarriages No history of birth available. At two months it was noted patient did not use left limbs well

P E At three and one-half years head 53.3 cm ; left arm very spastic, and smaller than the right, both legs somewhat spastic, the left leg is shorter than the right and seems more severely involved, no note of intelligence, poor history, family are very ignorant.

*Case 11 (Ped 24313)*

F. S , first child, labor stated to have been normal, but no details available no birth injury noted, never used left arm or leg well

P E At five years head normal size, left arm very spastic and smaller than the right, both legs slightly spastic, the left one worse, mental condition not noted

All five of these cases showed essentially a well marked hemiplegia (with greater involvement of the arm than the leg) complicated by a spastic weakness of the opposite leg which was not so severely affected as the homolateral leg. It is unfortunate that no observations upon the pathological anatomy are available and that the histories were not very satisfactory. However, a history indicative of possible birth injury was secured in several cases and it seems probable that most of these cases are true birth palsies. A case of bilateral spasticity due to porencephalic cavities in both cerebral hemispheres is included in appendix D. The cavities are periventricular and very similar to the central porencephaly described by Schwartz

# C ANALYSIS OF 17 CASES OF CONGENITAL HEMIPLEGIA AND MONOPLÉGIA FROM THE HARRIET LANE HOME RECORDS

## Case 1 (Ped 7708)

C S No accurate information about birth, said to have weighed 12 pounds, series of convulsions at six days, never opened left eye, vomited frequently

P E At three weeks head was 40 cm, sutures were widely separated, left lid drooped, left pupil large, fixed, left eye turns out, weakness of left deltoid probably peripheral, head asymmetrical, left frontal region flattened, all tendon reflexes increased, general increase in muscular tone, much old

TABLE 2  
*Analysis of 17 cases of congenital monoplegia and hemiplegia*

	NUMBER
<i>Birth history *</i>	
Convulsions in first two weeks	4
Feeble nursing and respiration	5
Difficult labor	9
Precipitate delivery	1
Prematurity	1
<i>Heads</i>	
Microcephaly	0
Asymmetrical heads	4
<i>Paralysis</i>	
Hemiplegias	16
Monoplegias	1
<i>Epilepsy</i>	
Convulsions, focal	5

\* No history of birth was secured in 2 cases

blood in spinal fluid At two months head was 41 cm in circumference, spastic of the right arm and leg was noted, one general convulsion At three months head was 41 cm in circumference, no more convulsions, bright child, right sided weakness still evident At five months mental development seemed satisfactory Right arm and leg spastic, third nerve palsy all gone except for large pupil, head still asymmetrical

## Case 2 (Ped 29893)

I B, first child, instrumental delivery, did not breathe well, two large cephalhematomas, vomited blood for four days At nine months it was

noted that right arm and leg were not used normally, leg has improved more than the arm

P. E. At five years head normal size, moderately severe right hemiplegia, extremities on right are somewhat underdeveloped, mental condition not noted.

*Case 3 (Ped. 17855)*

L L, third pregnancy, born by spontaneous labor, no history of dystocia, first two pregnancies resulted in miscarriages, child never used right arm or leg well; otherwise seems normal

P. E. At one year, size of head not given, partial right hemiplegia, mental condition not noted, poor examination and history.

*Case 4 (Ped. 35242)*

A. O, first child, born at seven months by normal labor, never able to use right arm or leg well, mental development apparently normal, no convulsions noted.

P. E At twenty months head large, symmetrical, spastic weakness of right arm and leg with some under-development, child seems mentally normal.

*Case 5 (Ped. 38753)*

E D, third child, born by precipitate labor, very cyanotic, did not cry or nurse for three days, on the ninth day twitching on the left side of the face, left arm and leg were cold and blue from birth and patient never moved them much for six months, eyes were crossed, at four months focal convulsions started on the left side

P. E At seven years head 51 cm, in circumference, left arm and leg weak and spastic, right external rectus weak, mental condition not obviously subnormal.

*Case 6 (Ped. 23418)*

B. E, first child, born by long difficult labor, forceps extraction, head lacerated, occiput flattened, probable fracture of skull, convulsions for six days, never used right arm and leg well, mental development fairly good, passed at school, infrequent focal convulsions on right, starting at six years

P. E. At eleven years head 53.5 cm in circumference, speech difficult, moderately severe right hemiplegia; mental development nearly normal.

*Case 7 (Ped 16279)*

M A , third pregnancy, forceps delivery at term, labor lasted sixty hours, right ear and scalp cut, left facial paralysis apparently peripheral, always dragged right leg and never used right arm well

P E At two years head normal size mental condition normal, slight residuum of right hemiplegia

*Case 8 (Ped 4113)*

G H , full term labor terminated by forceps, did not cry for several days, did not nurse, when child was only a few months old it was noted that the left arm and leg were not used well.

P E At five years partial left hemiplegia with under-development intelligence normal, head normal size

*Case 9 (Ped 8494)*

I K , first child born by difficult labor, forceps used, birth weight fourteen pounds, laceration of right side of head, convulsions on second day, weakness of left arm and leg noted at age of three months

P E At two years head of normal size, old depressed fracture on right side, partial left hemiplegia, not much difference in size of extremities on two sides, mental development only slightly retarded

*Case 10 (Ped 40459)*

F G , first child, born at term (?) by difficult high forceps extraction, birth weight 4 pounds, child never used right arm and leg well

P E At twenty-two months head of normal size, no difference in size of limbs yet apparent, severe right hemiplegia, no convulsions noted, mental condition not noted

*Case 11 (Ped 4787)*

E G , fifth child, born by full term normal labor, development retarded, did not walk until age of two years, talked at two years and three months, never used right arm and leg well

P E At six years head 50 cm in circumference, mental condition normal, severe right hemiplegia with underdevelopment of extremities on right.

*Case 12 (Ped 6577)*

H L , sixth child, full term, normal labor, weight 8 pounds, did not walk or talk until age of two years, weakness of right arm and leg noted at age of

eight months, probably congenital, focal convulsions started on right at age of two years

P. E. At eight years, head 48 cm in circumference, right arm and leg spastic and poorly developed, some mental defect—Binet Simon mental age of 7.4 years, internal strabismus

*Case 13 (Ped 32123)*

J S, fourth pregnancy, twin died at seven months in convulsions, fifth pregnancy died during delivery, first three living and well, child born by normal labor at term, weakness of right arm and leg noted as soon as child began to use them

P. E. At four years head of normal size mental condition normal right arm a little spastic, both legs are used normally

*Case 14 (Ped 38870)*

C. Z, first child, born at seven months by difficult forceps extraction, poor history of birth, weakness of right arm and leg noted when child began to use them, left arm was thought to have been weak at first

P. E. At two years head of normal size, partial right hemiplegia, no obvious difference in size of extremities on the two sides, mental development fairly good.

*Case 15 (Ped 43811)*

G C, first child, born by difficult forceps delivery, forehead cut, never used right arm or leg well, onset of focal convulsions at three months on the right side

P. E. At eight months head 44.5 cm in circumference, symmetrical, tendency to internal strabismus, spastic weakness of right arm and leg, face very slightly involved, no obvious difference in size of extremities on the two sides, mental development seems good

*Case 16 (Ped 29454)*

W. W. K, twelfth child of healthy parents, said to have been born by normal labor, never used right arm or leg very well, focal convulsions on the right side at long intervals

P. E. At five years head 47.5 cm in circumference, right arm and leg very spastic and smaller than extremities on the left, mental condition not noted

*Case 17 (Ped 34876)*

E B, first child, full term forceps delivery, no other information about birth available, never used right arm or leg well

P E At fifteen months head large, right side flattened, internal strabismus, right arm and leg are weak and spastic, and somewhat underdeveloped, seems bright

## TWO CASES OF THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS

*Case 18 (Ped 42061, Path 8294)*

E E, birth spontaneous at term, lasted eighteen hours, deep asphyxia, did not breathe, revived with difficulty, next day general twitching, vomited, limbs flaccid, very ill

P E At twelve days flaccid paralysis of all limbs, becoming spastic in two days, general muscular twitching, fontanels flat, pupils small and fixed, internal squint, spinal fluid clear, longitudinal sinus not punctured, pneumonia and death at fifteen days

Pathological anatomy Thrombus in longitudinal sinus showing beginning organization, brain soft, not carefully examined, cannot be found for further examination

*Case 19 (Ped 44555)*

S M, tenth child, sibs all living and well, born by long dry labor, no signs of birth injury, on second day developed ecchymoses over face and trunk, vomited blood, on the fifth day left arm began to twitch and later the right arm was involved

P E At six days rhythmical twitching of all extremities, more evident in the left arm and leg, jaundice, fontanels sunken, no rigidity or definite paralysis, tendon reflexes all very active, no clonus, spinal fluid very yellow contained only 25 white cells, on attempt to puncture the superior longitudinal sinus it was found to be thrombosed, no blood secured but a firm resistance encountered, gradual recovery, well one month later

## D (A) ANALYSIS OF 100 AUTOPSIES OF HYDROCEPHALICS

*Case 1 (Path 7805, Surg 51254, 61185)*

A T, born by full term, normal labor, ill on second day, many convulsions, nearly died, right hemiplegia noted several months later, at one year convulsions returned and continued at variable intervals all life

P E At seven years head of normal size and shape, right eye turns



out, spastic weakness of right arm and leg which are smaller than on left, mental development only slightly retarded, can read and write, X-ray of head shows "extreme convolutional atrophy"

Operation Skull thick, under dura on left side there is a thick pigmented layer of fibrous tissue adherent to dura and to arachnoid, when this is removed pia-arachnoid is thick and opaque, cortex is excessively thin and

TABLE 3  
*Analysis of pathological anatomy in 100 cases of hydrocephalus*

CAUSE	TOTAL NUMBER	BLOCK AT			
		Iter	Foramina	Base	Unde- termined
Meningitis (still active)	34	6*	7	3	18
Adhesions in meninges	19†	0	14	5	0
Syphilitic meningitis	3	0	2	0	1
Occlusion of iter alone	14	14‡	0	0	0
Associated with congenital defect	19§	4	6	1	8
Spina bifida	16	4**	5	1	6
Encephalocele . .	3	0	1	0	2
Associated with porencephaly .	3††	2	0	0	1
Old subdural hemorrhage	2††	2	0	0	0
Fresh ventricular hemorrhage	2§§	2?	0	0	0
Nothing found . . . . .	4	0	0	0	4
Total	100	30	29	9	32

\* Sections of only one, iter "plugged" by inflammatory process

† Many of these cases were congenital

‡ Sections of 7 midbrains available 5 showed "malformed" iters, 1 iter was blocked by transparent septum, these 6 cases were congenital, a "plugged" iter was found in the 7th brain, in this case hydrocephalus followed meningitis

§ Intracranial hemorrhage was found in 4 of these

\*\* "Malformed" iter found in the one brain sectioned

†† Abstracted below

‡‡ Both show "plugged" iter, abstracted below

§§ Abstracted below.

scarred, tissue removed for microscopic examination showed fibrous tissue with old yellow pigment, i e , old organized blood clot, death after second operation to relieve hydrocephaly

Pathological anatomy Dura thickened and adherent over left hemisphere, all meninges bound together, cortex of left hemisphere very thin and nerve cells lacking, left ventricle enormous, rt and 3rd ventricles also enlarged, meninges on right delicate, aqueduct is plugged by a mass of

fibrous tissue, outlines of old aqueduct shown by many small ependymal lined channels, apparently not quite completely occluded, yellow pigment in meninges and ventricles

*Case 2 (Path 7170, Surg 57635)*

C S, born by normal labor, severe illness in first few days, left hemiplegia noted when child was a few months old. At six years developed left-sided convulsions, which continued

P E At seventeen years head of normal size and shape, slight left hemiplegia with under development of left arm and leg, vision poor, moderate optic atrophy, nystagmus, X-ray of head showed marked "convolutional atrophy," mental development nearly normal, very irritable at times

Operation Meninges greatly thickened and adherent over right hemisphere, cortex reduced to a shell, dense adhesions at the base. Death

Pathological anatomy Bilateral internal hydrocephalus, right temporal lobe reduced to 5 mm thickness, merely glial tissue, no nerve cells, meninges thickened and adherent to cortex, left hemisphere shows only dilatation of ventricle, cortex averages 2 cm, meninges over left convexity are normal, iter is occluded by fibrous plug which is quite yellow, small channels lined by ependyma around margin of plug

These two cases are almost identical. The fact that the head was of normal size is against the possibility that these were cases of congenital hydrocephaly with birth injury. The "plugging" of the iter is also against that supposition. However, it is possible that a hemorrhagic encephalitis, or perhaps a local meningitis, in the first few days might have produced this picture

*Case 3 (Ped 45349, Path 8785)*

M W, first child, born at term, difficult delivery, in labor thirty-six hours, cried at once, nursed well for week, then stopped, vomited blood, blood in stools, very ill

P E At two weeks, head 37 cm sutures separated, bulging fontanelles irregular respiration, bilateral internal squint, weak and flaccid, ventricular puncture difficult, ventricles small, contain altered blood, cistern and spinal puncture also give altered blood, several transfusions, pressure symptoms vary, at one month head only 38 cm ventricles large, death

Pathological anatomy Moderate internal hydrocephalus, old blood in ventricles and subarachnoid spaces, iter full of clot

The intracranial hemorrhage was probably due to hemorrhagic disease

out, spastic weakness of right arm and leg which are smaller than on left, mental development only slightly retarded, can read and write, X-ray of head shows "extreme convolitional atrophy"

Operation: Skull thick, under dura on left side there is a thick pigmented layer of fibrous tissue adherent to dura and to arachnoid, when this is removed pia-arachnoid is thick and opaque, cortex is excessively thin and

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Occlusion of iter alone .	14	14‡	0	0	0
Associated with congenital defect	19§	4	6	1	8
Spina bifida	16	4**	5	1	6
Encephalocele .	3	0	1	0	2
Associated with porencephaly	3‡‡	2	0	0	1
Old subdural hemorrhage	2‡‡	2	0	0	0
Fresh ventricular hemorrhage	2§§	2?	0	0	0
Nothing found	4	0	0	0	4
Total	100	30	29	9	32

\* Sections of only one, iter "plugged" by inflammatory process

† Many of these cases were congenital

‡ Sections of 7 midbrains available 5 showed "malformed" iters, 1 iter was blocked by transparent septum, these 6 cases were congenital, a "plugged" iter was found in the 7th brain, in this case hydrocephalus followed meningitis

§ Intracranial hemorrhage was found in 4 of these

\*\* "Malformed" iter found in the one brain sectioned

‡‡ Abstracted below

‡‡ Both show "plugged" iter, abstracted below.

§§ Abstracted below

scarred, tissue removed for microscopic examination showed fibrous tissue with old yellow pigment, i e, old organized blood clot, death after second operation to relieve hydrocephaly

Pathological anatomy Dura thickened and adherent over left hemisphere, all meninges bound together, cortex of left hemisphere very thin and nerve cells lacking, left ventricle enormous, rt and 3rd ventricles also enlarged, meninges on right delicate, aqueduct is plugged by a mass of

fibrous tissue, outlines of old aqueduct shown by many small ependymal lined channels, apparently not quite completely occluded, yellow pigment in meninges and ventricles

*Case 2 (Path 7170, Surg 57635)*

C S, born by normal labor, severe illness in first few days, left hemiplegia noted when child was a few months old. At six years developed left-sided convulsions, which continued

P E. At seventeen years head of normal size and shape, slight left hemiplegia with under development of left arm and leg, vision poor, moderate optic atrophy, nystagmus, X-ray of head showed marked "convolutional atrophy," mental development nearly normal, very irritable at times

Operation. Meninges greatly thickened and adherent over right hemisphere, cortex reduced to a shell, dense adhesions at the base. Death

Pathological anatomy. Bilateral internal hydrocephalus, right temporal lobe reduced to 5 mm thickness, merely glial tissue, no nerve cells, meninges thickened and adherent to cortex, left hemisphere shows only dilatation of ventricle, cortex averages 2 cm, meninges over left convexity are normal, iter is occluded by fibrous plug which is quite yellow, small channels lined by ependyma around margin of plug

These two cases are almost identical. The fact that the head was of normal size is against the possibility that these were cases of congenital hydrocephaly with birth injury. The "plugging" of the iter is also against that supposition. However, it is possible that a hemorrhagic encephalitis, or perhaps a local meningitis, in the first few days might have produced this picture

*Case 3 (Ped 45349, Path 8785)*

M W, first child, born at term, difficult delivery, in labor thirty-six hours, cried at once, nursed well for week, then stopped, vomited blood, blood in stools, very ill

P L. At two weeks, head 37 cm sutures separated, bulging fontanels irregular respiration, bilateral internal squint, weak and flaccid, ventricular puncture difficult, ventricles small, contain altered blood, cistern and spinal puncture also give altered blood, several transfusions, pressure symptoms vary, at one month head only 38 cm ventricles large, death

Pathological anatomy. Moderate internal hydrocephalus, old blood in ventricles and subarachnoid spaces, iter full of clot

The intracranial hemorrhage was probably due to hemorrhagic disease

rather than to birth injury. However, the fact that the ventricles were small at first and the head enlarged slowly as compared to case 4, makes it probable that the hemorrhage was the cause of the hydrocephalus. It is questionable whether this child would have developed a chronic hydrocephalus if it had survived the acute stage.

*Case 4 (Ped. 45267, Path. 8811)*

A. R. K., fifth child of healthy parents, born at term by normal labor, head normal size, resuscitation difficult, never nursed well, vomited frequently

P. E. At seven days head 37 cm, some twitching of right arm, altered blood in cistern magna, at twelve days head 40.5 cm. vomited frequently, death on twenty-sixth day

Pathological anatomy: Extreme internal hydrocephaly, adhesions under base, blood in ventricles and subarachnoid spaces.

The rapid enlargement of the head suggests that this was a case of congenital hydrocephalus with a birth injury.

THREE CASES WITH PORENCEPHALIC CAVITIES

*Case 5 (Ped. 17182, Path. 5542)*

Baby S, born by full term normal delivery, breathed poorly, ill from birth, some blood in the stools, possibly hemorrhagic disease

P. E. At thirteen days head 39.5 cm, altered blood in the spinal and ventricular fluid, small encephalocele presenting through the anterior fontanel, blood Wassermann negative, at nineteen days head was 39.7 cm in circumference, death at five weeks

Pathological anatomy: Moderate thinning of the cortex, small cavity in left frontal lobe separated from ventricle by a perforated membrane, this corresponded to the position of the encephalocele, no explanation found for the hydrocephalus, no sign of syphilis, no spirochetes found

The rapid enlargement of the head strongly indicates that the hydrocephalus was present at birth, and the intracranial hemorrhage was an accidental complication.

*Case 6 (Ped. 13824, Path. 5098)*

G. H., only child of normal parents, birth by prolonged labor, two doses of pituitrin given, no forceps, head measurements unknown, stuporous on seventh day, grew stiff, stopped nursing, vomited, cyanotic at times until age of three months when vomiting started again.

P E At four months head 44 cm in circumference, marked general spasticity of extremities, more severe in arms, optic atrophy, no sign of mental development, death at five months

Pathological anatomy Gross, symmetrical cavities in both hemispheres, anteriorly these cavities are continuous with the ventricles and the cortex is reduced to a few mm in thickness, posteriorly the ventricles are not very large and the cavities are separated from the ventricles by a thin membrane—these cavities are lined by a rough glial surface, aqueduct is occluded, no sections could be found but from the description it seems that the aqueduct is "plugged"

*Case 7 (Pcd 42899, Path 8436)*

J W J, breech delivery, resuscitated with difficulty, always irritable and fretful, at one month was noted to be rigid and head was retracted, head seemed large at this time, at eight months twitching of the face and hands, vomiting and apparently headache

P E At six years, deaf-mute, head 53 cm in circumference, bilateral choked disc, tremor of head and both arms, roentgenogram showed signs of increased pressure, blood in ventricular and spinal fluids, "phthalein" test indicated obstructive type

Operation Aqueduct pin point aperture, dilated, no cause for bleeding found, hyperthermia and death

Pathological anatomy Bilateral papilledema, moderate hydrocephalus, multiple extra-ventricular cavities in temporal and parietal lobes,—these are bridged across by many fine trabeculae containing blood vessels, and lined by a rough glial membrane, only a thin layer of tissue separates them from the ventricles, the internal capsules are not interrupted, no signs of meningitis, aqueduct now patent because of surgical dilatation

(B) CLINICAL ANALYSIS OF 100 CASES OF HYDROCEPHALUS

CASE OF HYDROCEPHALUS POSSIBLY DUE TO BIRTH INJURY

*Case 1 (Pcd 24513)*

E H, third child of healthy parents, normal labor, no head measurements obtainable, convulsions at five days, development retarded in every way, another series of convulsions at three years

P E At five years head was 55 cm in circumference, right leg and arm and left leg spastic, severe mental defect, inability to speak, history unreliable, family ignorant and illiterate, diagnosis at least questionable

CASES OF HYDROCEPHALUS PROBABLY CONGENITAL ASSOCIATED WITH  
BIRTH INJURIES

*Case 2 (Ped 35967, Obs. 12319)*

J. C , second child, first pregnancy resulted in miscarriage, born by difficult version and extraction, hard to resuscitate, fractured skull and cephalhematoma, head measured 34 cm sub-occipito-bregmatic at birth

P. E. At one month head was 43 cm. in circumference, not quite

TABLE 4  
*Clinical analysis of 100 cases of hydrocephalus\**

	NUMBER
Syphilis . . . . .	3
Meningitis (observed) . . . . .	19
Meningitis (history) . . . . .	17
Associated congenital defect . . . . .	23
Spina bifida . . . . .	12
Encephalocele . . . . .	7
Chondrodystrophia . . . . .	2
Multiple bone defects . . . . .	1
Scaphocephaly . . . . .	1
Brain tumor . . . . .	3
Family history of hydrocephalus . . . . .	1
Possibly due to birth injury . . . . .	1†
No cause found . . . . .	33‡
	<hr/> 100

\* No autopsies, several operations

† Abstracted below.

‡ In 15 of these cases the history stated that the head was enlarged at birth, exact measurements usually not available In 4 of these 15 there was evidence of birth injury These are abstracted below

symmetrical, at two years and three months head was 58 cm in circumference, some weakness of left leg, tendon reflexes increased on both sides, mental development somewhat retarded, patient was over weight and larger than the average for age, hydrocephalus seemed arrested or only slowly progressive.

*Case 3 (Ped. 41412)*

C. B , third child of normal parents, born at full term by non-instrumental labor, nursed poorly, respiration feeble, several convulsions on fourth day, enlarged head noted at birth

P E At two months head enlarged not quite symmetrical, partial left hemiplegia, death at nine weeks

*Case 4 (Ped 22399)*

C R, third child of healthy parents, born by precipitate labor, head noted to be large and bones soft at birth, at three weeks head was greatly enlarged and "round," always nursed poorly, and was unresponsive, at seven weeks hydrocephalus was diagnosed

P E At two months head was 47 cm in circumference, little or no spasticity, ventricular puncture showed old blood in the ventricles, non-communicating type, at three months head was 49 cm in circumference, left hemiplegia was noted, convulsions, death at six months no autopsy

TABLE 5

*Analysis of 8 cases of congenital spastic paralysis in hydrocephalics due to birth injury*

	NUMBER
Monoplegia	1
Hemiplegia	5
Triplegia	1
Double hemiplegia (porencephaly)	1
	8

*Case 5 (Surg 53834)*

G F, born by difficult, instrumental labor, injury on left temple and over left eye, paralysis of left arm and leg, some squint, general muscular twitching, head 41 cm at birth, rapidly enlarged since

P E At three years internal squint of left eye, right pupil large and fixed, partial left hemiplegia, bilateral extensor response, head 56 cm, moderate mental defect

E ANALYSIS OF 8 CASES OF FOCAL EPILEPSY FROM THE SURGICAL RECORDS WITH OPERATIVE NOTES

*Case 1 (Surg 41240)*

R L G, born by difficult labor, head injured by forceps, no paralysis noted, general convulsions since the age of seven years, mental development has been fairly good

P E At age of eleven years head shows bulge in right fronto-parietal region, examination otherwise negative, no paralysis



Operation: Right craniotomy, bone thin, few dural adhesions, large yellow cyst replacing upper half of frontal lobe full of yellow fluid

Microscopic examination shows wall of cyst is composed of glial tissue covered by arachnoid, old blood pigment in wall

### *Case 2 (Surg 40710)*

W. U D , first child of healthy parents, born by long difficult labor which was terminated by high forceps, head cut by forceps, never used right leg normally, focal convulsions since age of one year

TABLE 6

*Analysis of 8 cases of focal epilepsy probably due to birth injury*

	NUMBER
<i>Birth history *</i>	
Convulsions in first two weeks ..	0
Feeble nursing and respiration	2
Difficult labor .	6
Precipitate delivery .	0
Prematurity . . . . .	0
<i>Heads</i>	
Microcephaly . ..	0
Asymmetrical heads	3
<i>Paralysis</i>	
Monoplegias . . .	2
Hemiplegias .. .	5
Hemianopia ..	1
No paralysis	1
<i>Pathological anatomy</i>	
Intracerebral cysts	3
Local cortical atrophy and scarring with thickening of overlying pia-arachnoid .	3
Organized subdural clot with atrophy of underlying cortex	1
Nothing found at operation	1

\* No history of birth was secured in 2 cases These histories were obtained in most cases many years after birth and consequently do not obtain as much information about early infancy as the Harriet Lane Home histories

P E At the age of three years head normal size, depressed area in left frontal-parietal region, right leg somewhat spastic, mental condition slightly subnormal

Operation: Left craniotomy showed very vascular dura, and edema of the arachnoid, no other lesion found

Microscopic examination of bit of arachnoid removed showed normal meninges

*Case 3 (Surg 41660)*

W H, born by difficult labor, instrumental extraction, very difficult to resuscitate, head "injured," always weak on right side, focal convulsions since age of 18

P E At age of twenty-two head normal, mental condition slightly subnormal, severe right hemiplegia, underdevelopment of right arm and leg

Operation Left craniotomy, dura adherent to arachnoid, thickening of pia-arachnoid, atrophy of convolutions especially the precentral gyrus, large collections of yellow fluid in Sylvian fissure

Microscopic examination of piece of arachnoid removed showed great fibrous thickening and no sign of an inflammatory process

*Case 4 (Surg 50719)*

C D P, second child of healthy parents, no definite history of birth obtained, never used left arm and leg normally, walked and talked late, infrequent convulsions on the right, always able to do his school work but not brilliant

P E At thirteen years in eighth grade, weakness and under development of left arm and leg, left homonymous hemianopia, slight sensory loss on left side

Operation Thin walled cyst in Sylvian fissure and right parietal region full of clear fluid, small opening into ventricle, meninges over this cystic area are greatly thickened and adherent

*Case 5 (Surg 51428)*

S E W, born by difficult forceps delivery, no injuries noted at birth, at age of two years focal convulsions started on the left side and a variable left hemiplegia was noted, mentally child progressed well

P E At five years head normal, seemed intelligent, left hemiplegia always severe after convulsion, but almost imperceptible at other times

Operation Dura thickened and adherent to a thick layer of fibrous tissue beneath it, this tissue was full of yellowish cysts and also adherent to the arachnoid, pia arachnoid thickened and cystic, moderate atrophy of convolutions beneath these cysts, central gyrus involved most severely

Microscopic examination of the layer of tissue found under the dura

showed only fibrous tissue and yellowish cysts, no signs of an inflammatory process, or of neoplasm

*Case 6 (Surg 55411)*

J. P. M., second child, birth normal as far as is known, never used right arm and leg well, focal convulsions at four years, more frequent since eight years, mental development fair, did moderately well at school

P. E. At seventeen years head normal, right arm spastic and under-developed, right leg shows very little weakness, slight mental defect

Operation Dura normal, huge cavity traversed by trabeculae, no communication with ventricle, opens into Sylvian fissure.

*Case 7 (Surg 63376)*

W. V., first child, forceps delivery, very difficult, head deformed, right eye prominent, left eye sunken in, walked at twenty-two months, talked at two years and six months, focal convulsions on left at two years, left arm and leg small, after each convulsion complete left hemiplegia

P. E. At eight years head large, large depression to right of sagittal suture, left arm and leg smaller than right, but strength only slightly diminished, some mental defect

Operation Dura adherent over right hemisphere and thickened, pia-arachnoid thickened, central convolutions atrophied, in this area cortex was only one cm thick and scarred and dense

*Case 8 (Surg 64089)*

T. S., born by difficult delivery, high forceps, difficult to revive, deep cyanosis, walked at fourteen months, but never used right arm or leg well, focal convulsions on right at nine years, right hemiplegia after each attack, mental development fair, in seventh grade at twelve.

P. E. At thirteen years head normal, slight spastic weakness of right arm and leg, right arm and leg under-developed

Operation Pia-arachnoid thickened over central gyri and angular gyrus, convolutions atrophied and scarred, microscopic examination showed extensive scarring of cortex and thickening of meninges, old blood pigment

REFERENCES

- (1) WEYHE Dissertation, Kiel, 1889
- (2) SPENCER, H. B. Obstet Soc London, 1892, 33, p. 203
- (3) SCHOTT Arch f Gynak, 1920, 2, p. 316
- (4) DELUCA, F. A. Semana Med, 1921, 29, p. 45

- (5) SCHAFER Zeitschr f Geburtsh u Gynäk, 1921, p 239
- (6) ARCHIBALD Amer Pract Surgery, 1909, 5, p 208
- (7) WARWICK, M Amer Jour Medical Science, 1919, 158, p 95, Amer Jour Disease of Child, 1921, 21, p 448
- (8) PIERSON, R N Surg, Gyn and Obstet, 1923, 37, p 802
- (9) CROTHERS, B Surg, Gyn and Obstet, 1923, 37, p 790
- (10) YLPPÖ Klin Wochschr, 1922, 1, p 1241, Zeitschr f Kinderheilk, 1924, 38, p 32
- (11) HOLT AND HOWLAND "Diseases of Infancy and Childhood," New York, 1919
- (12) DOEHLE Verh d 10, Internat Med Kongr 2, Berlin, 1890, Bd V 17, S 40
- (13) KUNDRAT, H Wiener Klin Wochschr, 1890, 46, p 887
- (14) SHARPE, W Jour Amer Med Assoc, 1923, 81, p 620  
SHARPE, W, AND MACLAIRE, A S Surg, Gyn and Obstet, 1924, 38, p 200, Amer Jour Obstet and Gyn, 1924, 8, p 186, Amer Jour Obstet and Gyn, 1925, 9, p 452, Surg, Gyn and Obstet, 1925, 41, p 587
- (15) ROBERTS, H Jour Amer Med Assoc, 1925, 85, p 500
- (16) McNUTT, S J Amer Jour of Obstet, 1885, 18, p 73
- (17) CUSHING, H Amer Jour Med Science, 1905, 130, p 563
- (18) BENEKE Münch Med Wochschr, 1910, 57, p 41
- (19) SIETZ Zentralblatt f Gynäk, 1912, 36, p 1, Arch f Gynäk, 1907, 82, p 529
- (20) SCHWARTZ, P Ztschr f d ges Neurol u Psych, 1924, 40, p 263
- (21) FISCHER Schweiz Med Wochschr, 1924, 54, p 905
- (22) SIEGMUND, H Münch Med Wochschr, 1923, 70, p 137
- (23) BALLANCE AND BALLANCE Lancet, 1922, 203, p 1109
- (24) CROTHERS, B Amer Jour Med Science, 1923, 165, p 94
- (25) BALLANTYNE, J W Edinburgh Med Jour, 1920, 25, p 63
- (26) EASTMAN Boston Med and Surg Jour, 1913, 168, p 165
- (27) STUMP AND SICHERER Beiträge z Geburtsh u Gynäk., 1909, 13, p 408
- (28) PAUL Inaug Diss Halle, 1900
- (29) JACOBS, M Jour Amer Med Assoc, 1924, 83, p 1641
- (30) VOSS Zeitschr f Hals Nasen u Ohren, 1923, 6, Congressbericht.
- (31) CAPON, N B Jour of Obstet and Gyn of British Empire, 1922, 29, p 572
- (32) BUZZARD AND GREENFIELD "Pathology of the Nervous System," 1923
- (33) SACHS, B "Nervous Diseases of Children," 1895
- (34) SYMONS, C P Quart Jour Med, 1924, No 69, p 93
- (35) PUTNAM, T, AND CUSHING, H Arch of Surgery, 1925, 11, p 329
- (36) SHARIF, W "Diagnosis and Treatment of Brain Injuries," 1920
- (37) CAMPBELL, A W Brain, 1905, 28, p 367
- (38) TREDGOLD, A F Arch of Neurol, 1903, 2, p 328
- (39) BURHAM AND GERSTENFELDER Jour Amer Med Assoc, 1923, 80, p 604
- (40) COLLIER, J S Brain, 1905 28, p 367
- (41) HOLLAND, L Jour Obstet and Gyn of British Empire, 1922, 29, p 549
- (42) GREENWOOD, W O Jour Obstet and Gyn of British Empire, 1924, 31, p 611
- (43) HUPFEST, H Amer Jour Dis Child, 1923, 26, p 503
- (44) DANDY, W F Ann Surg, 1919, 70, p 129
- (45) GPFEL, T M Surg Gyn and Obstet., 1922, 25, p 524
- (46) PIKE, STUART, GUTHRIE, AND BURNS Jour Exp Med, 1906, 8, p 289  
PIKE AND GOMFZ Jour Exp Med, 1909, 11, p 257

- (47) COUVELAIRE "Hemorrhages du System Nerveux Central des Nouveau Nés dans les accouchements par les forceps," 1907, s 4, 11, 7
- (48) BROWNE, F J Edinburgh Med Jour , 1921, N S 27, p 153
- (49) RAIZ Zentralblatt f Gynak , 1922, 46, p 524 (abstr )
- (50) GREEN, R M , AND SWIFT, J B Boston Med and Surg Jour , 1911, 164, p 454.
- (51) FOOTE, J A Amer Jour Dis Child , 1920, 20, p 18
- (52) KAISER New York State Med Jour , 1922, 116, p 156
- (53) CRUIKSHANK Lancet, 1923, 204, p 836
- (54) RODDA, F C Jour Amer Med Assoc , 1920, 75, p 452, Amer Jour Dis Child., 1920, 19, p 269
- (55) BRISSAUD Trâté de Medecine par Charcot, Bouchard et Brissaud, t VI, 1894
- (56) DEJERINE Rev mens de mal de l'enf , April, 1892, Soc de Biol , March 13, 1897
- (57) HEDREN, G Amer Jour Dis Child , 1918, 18, p 290 (abstr )
- (58) COTARD "Étude sur l'Atrophie partielle du Cerveau," 1863, Paris
- (59) GIBB Lancet, 1858, 30, p 468
- (60) OSLER, W Teratologia, 2, No 1
- (61) CAMERON, H C Lancet, 1923, 205, p 1292
- (62) HENKLE Zentralblatt f Gynak , 1922, 46, p 129
- (63) SCHULE Monatschr f Kinderheilk , 1923, 26, p 43
- (64) MANTON, W P New York State Med Jour , 1914, 14, p 302
- (65) BURR, C W Amer Jour Dis Child , 1921, 21, p 529
- (66) STILL Lancet, 1923, 204, p 431
- (67) KIRKWOOD AND MEYER Lancet, 1923, 205, p 65.
- (68) CUSHING, H Keen's Surgery, 1908, Vol 3
- (69) GILLES, R Rev mem de gynce, d'obstet , et de paediat, 1912, 7, p 465.
- (70) SIMMONS, C C Boston Med and Surg Jour , 1912, 166, p 43
- (71) GREEN, R M Boston Med and Surg Jour , 1916, 174, p 947
- (72) LIPPMAN New York State Med , Jour , 1916, 103, p 263
- (73) BRADY, J M Jour Amer Med Assoc , 1918, 71, p 347
- (74) VAGLIO, R Pediatrics, 1921, 29, p 12
- (75) MUNRO, D Read before Amer College of Surgeons, Boston, October 24, 1922
- (76) LITTLE, W J Trans Obstet Soc London, 1862, 3, p 293
- (77) McNUTT, S J Amer Jour Med Science, 1885, 89, p 58
- (78) GOWERS, W "Diseases of the Nervous System," 1907
- (79) MARFAN Presse Medicale, 1894, January 13, p 9
- (80) RAYMOND Maladies du Systeme Nerveux, Paris, 1894
- (81) TAYLOR, J Allbutt and Rolleston Systeme of Medicine, 2nd ed
- (82) OSLER, W "The Cerebral Palsies of Children," 1889
- (83) CAMERON AND OSMAN British Med Jour , 1925, 1, p 363
- (84) SACHS, B Amer Jour Med Sc , 1926, 171, p 376  
SACHS, B , AND HAUSMAN, L "Nervous and Mental Disorders from Birth through Adolescence," 1925
- (85) MARIE, P Leçons sur les maladies de la moelle, 1892
- (86) VAN GEHUCHTEN Rev Neurol , 1897, fev 15
- (87) FREUD, S "Die infantile Cerebrallahmung," 1897
- (88) FLER Über Angeborene spastische Gliederstarre, 1890, Basle
- (89) KRAFT-EBING Weiner Klin Wochschr , 1892, 47, p 681
- (90) NEWMARK Pacific Med Jour , 1894, July

- (91) PELITZAEUS, FR Arch f Psychiat, 1885, 16, p 698
- (92) COLLIER, J S Brain, 1924, 47, p 1
- (93) BUCHARDT (Quoted by Manton)
- (94) BEATUS (Quoted by Manton)
- (95) HANNES, W (Quoted by Manton)
- (96) HAMMARBERG Studien u Klin u Path der Idiotie, 1895
- (97) GANGHOFNER Ztschr f Heilk, 1896, 17, p 203
- (98) SPILLER, W S Jour Nerv and Ment Dis, 1898, 25, p 81, Univ Penn Med Bull, January, 1905
- (99) RHEIN, J H Amer Jour Med Science, 1909, 138, p 885, Jour Nerv and Ment Dis, 1913, 40, p 639
- (100) BISWANGER Virchows Arch f path Anat. u Physiol u Klin Med, 1882, p 427
- (101) GERLICH Arch f Psych, 1891-2, 23, p 203
- (102) OTTO Arch f Psych, 1891-2, 23, p 153
- (103) HAUSHALTER AND COLLINS Compt rend de la soc de Biol, 1905, 59, p 223
- (104) BATTEN, F W "Diseases of Children," by Garrod, Batten and Thursfield, 1913
- (105) HOLMES AND SARGENT British Med Jour, 1915, 11, p 493
- (106) CUSHING, H British Jour Surg, 1918, p 511
- (107) WILSON, G Arch Neurol and Psychiat, 1923, 10, p 668
- (108) VOGT, C U O J Psychol u Neurol, 1925, 31, p 256
- (109) VOGT AND ROSENBERG, O Berl Klin Wochschr, 1913, 50, p 2272, Ergebn d inner Med u Kinderheilk., 1921, 20, p 549
- (110) ROSS, S G Canadian Med Jour, 1924, 14, p 519
- (111) MACLAIRE, A S Jour of Nerv and Ment Dis, 1925, 62, p 498
- (112) FRASER AND DOTT British Jour of Surg, 1922-3, 10, p 165
- (113) WEED, L H Physiological Reviews, 1922, 2, p 171
- (114) DANDY, W L, AND BLACKFAN Amer Jour Dis Child, 1914, 8, p 406, Amer Jour Dis Child, 1917, 14, p 424
- DANDY, W L Ann of Surgery, 1918, 68, p 569, Ann of Surgery, 1919, 70, p 129, Surg Gyn and Obstet, 1920, 31, p 340, Surg Gyn and Obstet, 1921, 33, p 112, Johns Hopkins Hosp Bull, 1921, 32, p 67, Johns Hopkins Hosp Bull, 1922, 33, p 189
- (115) SPILLER, W W Amer Jour of Med Science, 1902, 124, p 44
- (116) SCHLAPP AND GFRE Amer Jour Dis Child, 1917, 13, p 461, Proc New York Path Soc, 1911, p 64
- (117) GUTHRIE, L S Practitioner, 1910, 85, p 47
- (118) BLACKF, J A Jour Comp Neurol, 1900, 10, p 79
- (119) HEUSER, C H Amer Jour Anat., 1913-14, 15, p 215
- (120) SOUTHWARD AND THOM Contributions from the State Board of Insanity, Mass, No 46, 1915
- (121) I EVY, D M, AND PATRICK, H T Jour Amer Med Assoc., 1924, 82, p 375
- (122) POLLACK, E Arb a d Neurol Ins Wien, 23, II 1, 118
- (123) GENTLY, I Jour Nerv and Ment Dis, 1925, 62, p 322 (abst)
- (124) CLARK, L P AND PROUT, T P Amer Jour of Insanity, 1905, 61, p 81
- (125) LEWIS, B "Text Book of Mental Diseases," 1890
- (126) KOTTER, H Ztschr f d ges Neurol u Psych, 1924, 93, p 791
- (127) REICHAERT, WUTH, STIFELMEYER, AND RUDIN Ztschr f d ges Neurol u Psych, 1924, 89 p 321

- (128) MEYER, A Medical News, 1903, July 18.
- (129) TURNER, W A Jour Neurol and Psych , 1923, 3, p 309
- (130) CADWALADER, W.A. Arch neurol and Psych , 1925, 14, p 358
- (131) DANDY, W E Johns Hopkins Bull , 1923, 34, p 245
- (132) WILSON, S A K Jour Neurol and Psychopath , 1923, 4, p 133.
- (133) SPRATLING "Epilepsy and Its Treatment," 1904
- (134) POTTS, C Medical Clinics of North America, 2, p 849
- (135) BEACH AND SHUTTLEWORTH Allbutt and Rolleston System of Medicine, 2nd ed.
- (136) BOLTON, J. S Arch Neurol , 1903, 2, p 328

## John Howland

February 3, 1873-June 20, 1926

Many persons who are very gifted and who devote themselves without stint to their tasks in life gain grateful appreciation of their service to mankind and of their betterment of knowledge. To only a few, however, is given in addition that warmth of enthusiasm and of human sympathy that kindles the divine fire in others and thus, through the inspiration that such natures inevitably give, carries on their influence when they are gone.

Gracious personality, elevated character, distinguished intellect, all these are needed to make the most effective men. There comes occasionally into one's life a personality that excites an instant sense of vivid, eager, gracious charm. Sometimes it proves that these magnetic gifts are worn only as an outer garment and only in the superficial relations of life. With rare individuals there is an equally immediate and magnetic feeling that these qualities come surely from within and are founded upon still more precious things, generosity, sincerity, upright truth.

John Howland's original American forbear and his fellow Pilgrims brought to this land unbending devotion to the right as they saw it. This frequently passed down to their descendants. It has often lent to their view of the proper conduct of life a touch of severity that sometimes tries natures of softer kind but that goes far toward explaining the large part many of them have played in fine progress. A share of this Howland had in severe judgment of himself and his work, in relentless, patient purpose and determination. It had to do with the untimely end, sense of duty made him wholly unremitting in work and unsparing of himself.

But in him the Puritan was dominant only in his sense of responsibility. He had other spiritual ancestry. He owed

To one the cool and reasoning brain,  
To one the quick, unreasoning heart



He chose work with little children not merely as an interesting and fruitful field of effort, but because he loved to minister to their dependence and innocence. He sought and made and held friends ardently, loyally and with outgiving spirit.

He loved the beautiful, particularly the out of doors, and especially the lovely New England hills that his ancestors came from and amongst which he now lies.

As a companion or teacher he was vivid, humorous, stimulating, full of imagination, informed in many and wide ways.

He rejoiced in books, especially in books of biography and history of the very human kind, and in medicine and related science he sought with eagerness and appreciation the information that reading gives. As a teacher it was a joy to him to carry this on to others and his own happiness in scholarly things and his generous spirit of service to others were the origin of this journal. To it, taxed as he was by other duties, he devoted constant thought, patient, detailed effort and unending enthusiasm. The idea that led to it was his, as were the heavy efforts necessary to carry it past the inevitable early difficulties of so unusual an undertaking, and it was his broad knowledge that recognized which discussions were needed and which would be fruitful.

With such gifts as he had, with intense industry, with high purpose, with joy in human service it was but natural that he had no superior as a physician to children, that he inspired students and staff, and that he left disciples in high places in many parts of the land. Beyond these accomplishments he added to knowledge in ways that will endure, and he began and determined throughout this country, a transformation in the methods of studying, of teaching and of investigating the subject that was his life's work.

On the entrance to one of our universities is the inscription

Enter this gateway and seek  
The way of honor  
The light of truth  
The will to work for men

He entered life treading the way of honor, he sought ever the light of truth, the will to work for men controlled his life.

# ACTIONS AND USES OF THE SALICYLATES AND CINCHOPHEN IN MEDICINE

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## INTRODUCTION

This summary covers all the available literature since the introduction of the salicylates and cinchophen into medicine, that is, during the period of the last half century. It is based on a previous summary published twelve years ago in the annual (1914) report of the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association, and is essentially an amplification with revisions and additions embodying the results of investigations to date. Since the first review, cinchophen has come into extensive use in the treatment of rheumatism and therefore has been included in this review.

The salicylates are among the most extensively investigated drugs, both experimentally and clinically. This is less true of cinchophen. The period from 1875 to about 1880 abounds in contributions dealing with studies on the antiseptic and general pharmacological actions of the salicylates. Their value in rheumatic fever had been recognized as early as 1876, but it is the later and more recent studies that have been concerned more directly with the therapeutic application in rheumatism and other diseases. There is no doubt that the studies of the past decade have changed our views regarding the specificity of the salicylates in rheumatic fever. However, it can not be said that there is as yet a complete agreement on the mechanism of their highly efficient symptomatic relief in this disease. After half a century of continuous and extensive trial, there is, therefore, still considerable need of investigation of their actions.

There are also economic and health aspects to the usage of these drugs which indicate the desirability of all possible information. Probably indiscriminate medication with the salicylates and cinchophen exceeds the proportions with all other drugs. This is indicated by their extensive popularity in the relief of headaches, colds, neuralgias, etc. Many persons become addicted to the use of small doses over long periods in the treatment of minor complaints, while the dosage in rheumatism and kindred disorders is generally large, or massive. The public health aspect of mass drugging with these agents, therefore, would seem to merit some attention.

The salicylates are the sovereign remedies in the treatment of rheumatic fever, a disease with most serious economic aspects. The Ministry of Health in England (1) has ascertained that nearly one-sixth of the industrial invalidity in that country is due to rheumatism and that the loss to the nation is over three million weeks of individual work from the insured population and an estimated loss of £2,000,000 (about ten million dollars) to the beneficiaries. In this country, the United States Public Health Service (2) has ascertained that acute rheumatism was third in the list of sixteen principal causes of disability in 1924 among male wage earners in different industries. The number of cases was exceeded only by one disease, namely influenza, as the first principal cause, and by non-industrial accidents as the second cause. Rheumatism is also one of the most important causes of cardiac disorders. Falkner and White (3) estimate that 95 per cent of the cases of heart disease in young people can be traced to rheumatic fever and chorea. Despite the therapeutic use of these drugs in rheumatic fever, there remains the large incidence of cardiac disease directly traceable to it. This naturally raises the question of their therapeutic efficiency in this disease, which merely raises the ultimate question of how well their actions and uses are understood, their limitations, the possibilities of doing more harm than good, etc. Therefore, if this review will add to the knowledge and assist future investigators of these drugs, the effort spent upon it shall have been adequately compensated.

In general, meticulous details have been avoided, but the necessary objective data and results have been cited fully so as to leave no doubt of the basis for judgment or opinion. When decision has been im-

possible, the reader will have at hand at least the available sources of information. Owing to their importance, or to some special interest, certain topics have been purposely discussed in greater detail than others. The chronological order of development of the various topics has been maintained as much as possible, but this order has been waived when the topic merited development from another point of view. The references used in the text have been numbered throughout. Those that have not been used alphabetically, and have been appended to the bibliography for completeness. The originals of many of the latter were appeared without merit, and those on salicin where the drug is obsolete.

## CHEMICAL AND PHYSICS

The presence of salicyl in plants, discussed in the literature since the introduction of the salicylates into medicine, that was known long before the salicylates were used. It is based on a previous work from Salicylic acid ( $C_6H_4 \cdot OH \cdot COOH$ ) was first prepared (1914) report of the author (5) from salicin, which had been discovered in the Council on Pharmacy and Medicine in 1827 by Leroux (6). In 1844, Cahours (7) prepared it from gaultheria oil, but it was not until 1860 that Knab (8) prepared it synthetically from phenol by a Pinchophen has come into vogue today and therefore has the

The more important salicyl esters represent Methyl salicylate ( $C_6H_4 \cdot OH \cdot COOCH_3$ ) was investigated by Cahours (9) from oil of gaultheria, but now of sweet birch. Acetylsalicylic acid or "aspirin" ( $C_6H_4 \cdot COOH$ ), which is not an ester, was introduced into by Wohlgemuth in 1899 (10), and shortly afterward, its pharmacological action was described by Dreser (11). "aspirin" was coined from "spirsäure," an old German name for salicylic acid, the prefix "a" indicating "acetyl." Salicylosalicylic acid ("salsal" or "diplosal") ( $C_6H_4 \cdot COOH$ ), was introduced by Boehringer and Soehne in

The physical and chemical properties of salicylic acid, of their salicylate and acetylsalicylic acid are so well known that they need no description here. They may be found in the Tenth United States Pharmacopoeia (1926) in which these preparations are official.

at the end of 24 hours, in the most alkaline buffer mixtures used (pH 8.4). This might be expected, since, according to Furukawa (18), the water solubility is only 0.013 per cent.

The discoloration of solutions of sodium salicylate on standing has been known for a long time but is not understood. Except for inelegance, the change is of no practical importance in prescribing. The products formed do not appear to be toxic. There is, however, a loss of strength in such solutions, and this is due in part at least to the growth of fungi and possibly other organisms, for solutions of sodium salicylate or salicylic acid used as colorimetric standards for estimation of salicyl in foods, body fluids, excretions, etc., do not decompose when preserved with chloroform. Mixtures of bicarbonate and salicylate, frequently prescribed in the treatment of rheumatism, become nearly black and eventually deposit a black precipitate. According to Greenish and Beesley (25), this is due to the oxygen of the air acting in the presence of sesquicarbonate and is prevented considerably by the addition of about 0.013 per cent of sodium sulphite ( $\text{Na}_2\text{SO}_3$ ) or bisulphite ( $\text{NaHSO}_3$ ), or 1 grain to 8 ounces of the salicylate mixture. All of this indicates that the salicyl group is more readily destroyed than is generally assumed, and is of importance in connection with the fate of the compounds in the body. From the fact that lower forms of life thrive in, and even help to destroy, solutions of salicylic acid and sodium salicylate (26) their inefficiency as antiseptics is suggested.

Chemically, cinchophen or "atophan," is phenyl-quinoline carboxylic acid ( $\text{C}_6\text{H}_5\text{C}_9\text{H}_6\text{N}(\text{COOH})$ ). It was described by Doebner and Giesecke in 1887 (27) and introduced into medicine by Nicolaier and Dohrn in 1909 (28). It has a bitter taste and causes gastric disturbance owing to its acid character. Its solubility in water is low but this can be increased with the aid of an equal part of sodium bicarbonate or hexamethylenamine. The bicarbonate forms the soluble sodium salt and the hexamethylenamine, presumably the ammonium salt. The sodium salt is relatively non-irritating. A mixture of hexamethylenamine and cinchophen also contains free formaldehyde resulting from the decomposition of the hexamethylenamine. Therefore, this mixture, which has been advocated, would have no advantage from the standpoint of gastric irritation.



over cinchophen itself. Neocinchophen ("novatophan" or "tolysin") is the ethyl ester of methyl phenyl-quinoline-carboxylic acid ( $\text{CH}_3\text{-C}_9\text{H}_4\text{N-C}_6\text{H}_5\text{COOC}_2\text{H}_5$ ). It is not official. It is an odorless and tasteless yellow powder nearly insoluble in water, dilute alkalies and acids, but very soluble in lipid solvents. The tastelessness is due to its poor solubility, which also suggests poor absorption.

#### PHARMACOLOGICAL ACTIONS

##### *Antiseptic properties*

This is possessed by the salicylates to a limited extent only, being demonstrable with the acids in fairly high, and uncertain or inefficient with the salts in the highest concentrations. Accordingly they are weak protoplasmic poisons. The action is essentially bacteriostatic and not germicidal. In any case, free salicylic acid and the high concentrations of sodium salicylate necessary for antiseptic action are not demonstrable in any of the body fluids, except possibly in urine after full therapeutic dosage. Nothing is known of the antiseptic actions of cinchophen. The evidence presented below deals exclusively with the salicylates.

*Fermentation* In 1874, Kolbe (29) found that fermentation of cane-sugar was arrested by a 0.04 per cent solution of salicylic acid, a 0.4 per cent solution preserved fresh milk for 36 hours, 0.1 per cent salicylic acid interfered with the action of emulsin on amygdalin, with the formation of mustard oil, and it preserved minced flesh for a week. Feser (30) confirmed most of Kolbe's observations and, in addition, found that sodium salicylate possessed properties quite similar to those of the acid, although weaker. Muller (31) found salicylic acid in corresponding concentrations to be less active than phenol in preventing putrefaction of urine, but more energetic in preventing decomposition by amygdalin, sugar formation by liver, and peptic digestion. Schaer (32) observed that salicylic acid only mildly retarded the action of unorganized ferments, the activities of ptyalin and diastase were neither prevented nor weakened. Meyer and Kolbe (33) found that 0.25, 0.5 and 0.75 grams of salicylic acid inhibited 1, 15 and 55 grams of yeast, respectively, in 1 liter of sugar solution. The treated yeast remained inactive and the salicylic acid

did not undergo chemical change Cresotinic acid behaved about like salicylic acid According to Neubauer (34), the growth of penicillium is also inhibited by salicylic acid

Béchamp (35) observed that dilute solutions of salicylic acid modified the structure and suspended the functional activities of yeast, but did not kill them Kolbe (36) observed that the isomers of salicylic acid, i e , the meta- and para-oxybenzoic acids, its salts and the esters, salicin and saligenin had no antiseptic actions, but the cresotinic acids acted like salicylic acid This was confirmed nearly 40 years later by Stockman (37) who studied, in addition, some other compounds with the following results Salicylic acid in 1 5000 concentration delayed, while 1 2000 inhibited yeast fermentation, sodium salicylate had almost no action, the meta- and para-hydroxybenzoic acids required about ten times higher concentrations to produce effects similar to those of salicylic (ortho-hydroxybenzoic) acid and the following were not antifermentative, salicin (1 250), acetylsalicylic acid (1 250), dimethylsalicylic acid (1 1000) and salicyluric acid According to Fuhner (38), 1 cc of 0 02 per cent salicylic acid inhibits carbon dioxide production in a mixture containing 3 cc of yeast suspension, 4 cc of salt solution ( $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ , 0 2 per cent and  $\text{KHSO}_4$ , 0 3 per cent) and 2 cc of 4 per cent dextrose Under these conditions salicylic acid would seem to be more efficient as an antiseptic (concentration of about 1 50,000) than under ordinary conditions The test is claimed to be valuable in examination for food preservatives Comparing equimolecular solutions of sodium salicylate (1 per cent) and sodium acetylsalicylate (1 25 per cent) on yeast fermentation, Dreser (11) found that the sodium salicylate was about twice as efficient as the acetylsalicylate in diminishing the production of carbon dioxide However, when the 2 compounds were tested with *B coli* in milk, their antiseptic efficiency was about the same Both compounds caused definite injury to the organisms in both sets of experiments Taking into consideration the pH, Waterman and Kuiper (39) found that salicylic acid in from 0 04 to 0 06 per cent concentration at pH 4 8 to 4 4 was more efficient than benzoic acid at about the same pH in preventing the growth of penicillium glaucum The anions were not concerned with the checking influence, since much higher concentrations of the salts were ineffective, and the action

was ascribed to the lipid solubility of the undissociated molecules of the acids. This is probably the only work on salicyl antiseptics in which the influence of hydrogen ion concentration has been considered.

As for the sodium salt of novaspirin, this was found by Dreser (61) not to inhibit yeast fermentation. The same was observed by Corpe (40) with cresotinic acid which is related to salicylic acid.

*Seeds and roots.* Knop (41) observed that roots of maize plants and various plant seeds lost their reproductive properties in 0.07 per cent solution of salicylic acid. Salicylaldehyde appears to be more efficient, for Gardner (42) found that 10 parts per million in solution cultures reduced the growth of wheat plants 31 per cent during the first six days and the plants were killed in 50 parts per million. Other crops were affected similarly, though higher concentrations were necessary to cause injury to some. In soil cultures, 25 parts per million injured wheat seedlings. Certain bacterial cultures in which the aldehyde decomposed also did not grow.

*Putrefaction of flesh.* One per cent salicylic acid was found by Salkowski (43) to prevent the putrefaction of a mixture of putrid ascitic fluid and minced meat (incubated at 25° to 30°C) for eight days, in more highly concentrated solutions the mixtures were preserved for from four to five weeks. As soon as the mixture became alkaline, however, putrefaction ensued. This antiseptic action was exceeded by benzoic acid. Later, Salkowski (44) observed that 0.1 per cent salicylaldehyde prevented putrefaction and 0.25 per cent acted as disinfectant, this compound being more efficient than salicylic acid. Incubation of the pancreas with broth and phenyl salicylate (salol) was found to remain sterile by Lesnik (45). This was attributed to the decomposition of the ester into phenol and salicylic acid, since incubation of saliva, serum albumin and enzymes with salol resulted in the liberation of salicylic acid. Feser (30) found that flesh rubbed with salicylic acid did not putrefy for several weeks, and a putrid extract of meat when treated with double its volume of 0.4 per cent of salicylic acid solution produced no effect subcutaneously. Feser thought that salicylic acid acts less efficiently on chemical fermentation processes. In this connection, it may be stated that the presence of a salol-splitting ferment in human milk has been reported by Usener (46) on the ground that after administration of the ester,

salicylic acid could be detected in the stomach of a breast-fed infant one hour later

**Bacteria** Using a putrid tobacco infusion as bacterial emulsion, Bucholtz (47) found that bacterial growth could be prevented by salicylic acid (0.15 per cent solution), sodium salicylate (0.4 per cent), ammonium salicylate (0.416 per cent), and methyl salicylate (0.1 per cent by volume). Bacteria were killed in the shortest time by 1 per cent methyl salicylate, after a longer duration by 0.5 per cent solution and also by salicylic acid (0.35 per cent). Cech (48) found that higher dilutions than 0.1 per cent of salicylic acid did not inhibit the growth of bacteria. Koch (49) observed that 1:1500 of salicylic acid completely inhibited the *B. anthrax*, but after a month's application to the spores no harmful effects were observed. Heinz (50) quotes Lubbert to the effect that staphylococci required 1:655 of salicylic acid for complete inhibition. According to H. C. Wood, Jr. (51), the neutralization of salicylic acid by sodium and strontium lessens its bactericidal strength very materially. In his studies of different salicyl compounds, Stockman (37) found that *B. coli* kept in contact with a 1:1000 dilution of salicylic acid for three-fourths of an hour stopped the growth permanently, while the meta- and para-hydroxybenzoic acids required about ten times higher concentrations to produce similar effects. Sodium salicylate had almost no germicidal action and salicyluric acid was entirely inert.

**Urine** The putrefaction of urine is delayed after the direct addition or internal administration of sodium salicylate. Binz (52) noted that when carbon dioxide was passed through urine containing sodium salicylate, decomposition took place later than when the urine contained either the salicylate or carbon dioxide alone. The antiseptic effects were presumably due to liberated salicylic acid. Meyer and Kolbe (33) found that the addition of 1:2000 of salicylic acid to fresh urine delayed putrefaction so that the urine remained clear for three days and did not become ammoniacal. Fürbringer (53) stated that daily doses of 1 to 2 grams of salicylic acid rendered a urine acid which had exhibited ammoniacal decomposition in the bladder, and a beneficial effect was produced in the inflamed urinary passages.

Its limited antiseptic properties in urine are due to the fact that the salicylic acid is "bound" by the alkaline phosphate present. Meyer

and Kolbe found that 1 molecule of the disodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) "bound" two-thirds of a molecule of salicylic acid. They suggested that its limited antiseptic action in body fluids, in general, was because of their alkalinity. Prideaux (54) found that 0.5:1000 of salicylic acid added to urine would prevent the development of bacteria, 1.5:1000 would preserve it for several months and three to four parts per thousand killed bacteria in an infected urine. Sollmann (55) observed that, after a dose of 1 gram of the sodium salicylate, turbidity was slight or absent in the salicylate urine as compared with marked putrefaction in the same urine before the salicylate was taken. Smaller doses of salol (0.3 to 0.5 gram) delayed putrefaction for about 7 hours. Jordan (56) found that the antiseptic power of salicyl urines of high acidity (by titration) was somewhat greater than could be accounted for by an increase in the acidity alone. Jordan took 20 grains of salicylic acid per day and studied the acidity and putrefaction as well as bactericidal properties of samples of twenty-four specimens of urine. His data indicated that salicylate urine possessing about the same acidity as normal urine required practically once as long to become alkaline and nearly twice as long to become ammoniacal. When incubated with *M. staphylococcus* the urine became alkaline in about 2 to 10 days, depending on the acidity. Jordan stated that the normal acidity of urine is sufficient to liberate salicylic acid from sodium salicylate, but that administration of sodium salicylate only slightly increases the acidity of urine. He suggested that the antiseptic power of salicyl urines may be due to a change of proportions between the salicylic and salicyluric acids.

H. C. Wood, Jr. (57) found the efficiency of salicylic acid and salol as intestinal antiseptics limited, being easily surpassed by betanaphthol, formaldehyde and creosote.

#### *Local action and irritation*

The application of salicylic acid causes slow and practically painless destruction of the epithelium of the skin though it causes considerable superficial corrosion of mucosae. It is therefore rather irritating, causing nausea and vomiting when administered internally. For instance, Hodara (58) found that prolonged contact with the skin causes swelling of the epidermis followed by desquamation. The salts

are non-irritating even in high concentrations. The destructive action of salicylic acid on cells is made use of in preparations (ointments, collodions, etc.) for softening corns and warts, and in the treatment of certain skin diseases, alopecia, pruritus, etc. For eczema and dermatitis a 10 per cent ointment has been used by Berkenbusch (59). Repeated application of various salicyl preparations to skin was found by Sauerland (60) to cause hypersensitiveness resulting in eruption and the appearance of dermatitis in untreated areas. However, this is not peculiar to salicylic acid, for similar phenomena have been observed with a variety of irritants including chemical warfare compounds and the phenylenediamines. There is no sensitization in the anaphylactic sense, but rather an increased susceptibility of the skin and its capillaries to stimuli.

The irritant properties of different salicyl acids may be demonstrated by the method of Dreser (61). This consists of immersing tails of live fish into saucers containing the different solutions. A fish tail in tonus remains spread like a fan, but when depressed, it collapses and the fan shape is lost. Using this method, Dreser found that depression of fish tails was caused after immersion into a mixture of 4 cc. of 2.5 per cent sodium salicylate and 3 cc. of 0.25 per cent hydrochloric acid, but the control of hydrochloric acid alone produced no effect, indicating that the depression was due to the salicylic acid. Saturated solutions of acetylsalicylic acid also caused depression but not those of novaspirin. The solubility of the latter was too low for adequate concentration, but there was no doubt that the salicylic and acetylsalicylic acids were irritating.

### *Absorption*

*Cutaneous.* Salicylic acid and its esters in fatty and alcoholic solutions are readily absorbed from the intact skin. In 1876, Drasche (62) demonstrated that an alcoholic solution of salicylic acid applied to the skin caused the appearance of salicyl in the urine almost immediately. After the application of 20 to 30 grains of salicylic acid in olive oil to the axilla, Randolph and Dixon (63) found that the urines of six patients gave positive iron tests for salicyl. In one case enough salicyl was absorbed to relieve rheumatism. Bourget (64) made a quantitative study on the effect of different fatty bases, and the

effect of such factors as age, sex and disease condition on the cutaneous absorption of salicylic acid as judged by the excretion in urine. It was found that salicylic acid was rapidly absorbed from the skin. The rapidity of absorption and the amount depended on the vehicle, being most effective with lard or lanolin, least with vaseline and glycerol. The skins of old individuals were found to be less permeable than those of the young, also, skins of red haired and blond individuals absorbed more readily than those of dark haired. The skins of females were more readily permeable than those of males. These differences were attributed to differences in skins, but no cognizance was taken of interferences with renal function, as most of the patients were ill with acute rheumatic fever and other febrile conditions. Curative effects were obtained in rheumatic fever only. Linnoisier (65) suggested the volatility of salicylic acid at body temperature as the explanation for its absorption by the skin. According to Schumacher (66), the intact skin of the horse, calf, dog and rabbit is permeable to salicylic acid when applied as an ointment or in alcoholic solution, to sodium salicylate somewhat more readily in the form of ointment. However, Levin's study (67) indicates that no salicyl appears in the blood after the application of salicylate ointments to the skin.

The esters of salicylic acid are absorbed more readily than the acid itself or its salts. Linnoisier and Lannois (68) could detect salicyl in the urine 30 minutes after application of the esters to the skin. According to Floret (69), methyl-oxymethyl salicylate (mesotan) is readily absorbed by the skin, and saponified in the body. Impens (70) found that from 8 to 9 per cent of the methyl salicylate is absorbed, monoglycyl salicylate (spirosal) more readily, and to the greatest extent, that is, about one-sixth to one-fifth of the amount used, amyl salicylate, least effectively. Sauerland (60) found that about 0.5 per cent of the salicyl of the methyl salicylate in vaseline when applied to human skin is found in the urine, about 15.4 per cent with spirosal in lanolin, and 2.5 per cent with saligenin in lard and vaseline. Spirosal is practically non-irritant and can be used undiluted, while mesotan is irritant and should be diluted with one to four parts of olive or cotton-seed oil before application. Joachimoglu (71) reports that 24 hours after inunction of the thigh and leg with 10 grams of "rheumasan" (a soap mixture containing 10 per cent salicylic acid) salicyl was detectable in 10 cc of urine.

*Oral and nasal* Recently, Planelles (72) demonstrated qualitatively the presence of salicyl in urine from the smoke of cigarettes impregnated with salicylic acid and acetylsalicylic acid. The smoke was held in the mouth and nose, swallowing and inhalation being avoided as much as possible. Smoking in vitro of such cigarettes also showed the presence of the drugs in the smoke.

*Esophageal* Kuzaya (73) found that introduction of sodium salicylate into the esophagus ligated at the cardia resulted in the appearance of salicyl in urine at the end of 20 minutes, but when injected elsewhere salicyl was not excreted into the esophagus, apparently a case of one-sided permeability.

*Gastric* The absorption from the lower portions of the alimentary canal takes place much more rapidly than from the skin, mouth and esophagus. The data on gastric absorption of the salicylates are extremely limited, but Burow (74) asserts that the soluble salts are slowly absorbed, and the insoluble pass unchanged into the intestine. According to Breguet (75) alcohol facilitates the absorption of sodium salicylate from ligated stomachs of guinea pigs as compared with aqueous solutions. Of the esters, salol, being relatively insoluble, is not decomposed and absorbed in the stomach, but becomes immediately decomposed and absorbed when it reaches the intestine (Ewald (76)). Ethyl salicylate is claimed by Houghton (77) to be readily and quickly absorbed from the stomach.

*Intestinal* With small doses of the sodium salicylate the intestinal absorption is so rapid that no local antiseptic action occurs, according to Kumagawa (78). The effect of different vehicles on the absorption of sodium salicylate as judged by the excretion in urine was studied by Mastbaum (79). Alcohol did not influence and mucilaginous vehicles delayed the absorption as compared with aqueous solutions. Pinczower (80) finds that the absorption (as judged by the excretion in urine) of salicylic acid, sodium salicylate, acetylsalicylic acid, nov-aspirin, salol and salpyrin from the stomach and intestines presents no differences worthy of mention.

Nencki (81), Lesnik (15) and Bondzynski (82) thought that the esters of salicylic acid are practically entirely hydrolyzed in the intestine before absorption takes place. However, H. C. Wood and Hare (83) suggested that the greater toxicity exhibited by some of



these esters might be due to the absorption of the esters themselves Baas (84) claimed that the ethyl and methyl salicylates can pass into the urine combined with the ethereal sulphates, but not free. Convincing evidence that salicyl esters as such pass into the circulation was obtained in their studies on urinary excretion by Hanzlik and Prescho (24), who found up to about 0.12 per cent in urine of the clinical "toxic" dose (6.5 to 10.7 grams) of methyl salicylate but probably more was absorbed from the intestine. The urines possessed the odor of wintergreen. These investigators also found that about one-half the total salicyl salicylate and acetylsalicylic acid administered is absorbed, for from 8.8 to 36.6 per cent of the former (23) and 6 per cent of the latter (21) appeared unchanged in the urine. According to Buss (85), no salicyl appears in the urine in one hour after the administration of salicin.

*Hydrolysis of esters in the stomach and intestine* The reason for the considerable absorption of unchanged esters is that hydrolysis with the liberation of salicylic acid proceeds slowly in the alimentary tract. This is indicated by the results of the incubation experiments of Hanzlik and Prescho (21, 23, 24) detailed under "chemical properties," and also by the excretory results just mentioned. The significant results of the incubation experiments were as follows. Liberation of salicylic acid from acetylsalicylic acid in buffer mixtures of the same degree of acidity as in gastric juice and of alkalinity as in intestinal juices was about equal at the end of one hour, i.e., about 5 per cent, and this was increased to 35 and 45 per cent in the acid and alkaline mixtures, respectively, at the end of 18 hours. About 98 per cent of the drug remained undecomposed at neutrality (pH 7.0) at the end of 1 and 18 hours, and about 45 per cent at the end of 24 hours. Accordingly, liberation of free salicylic acid in the stomach would be expected, contrary to the claims. On the other hand, the claims made for poor gastric liberation of salicylic acid from salicyl salicylate appear to be justified, since the liberation was almost negligible in acid buffers. At the end of one hour 97 per cent of this ester was left unhydrolyzed in buffer mixtures possessing the alkalinity of blood (pH 7.4), and about 92 per cent at the end of 6 and 24 hours in mixtures with alkalinity (pH 8.0 to 8.4) corresponding to that of intestinal juices. Bile and pancreatin did not increase the hydrolysis. The weakest hydrolysis

occurred with methyl salicylate, for no liberation of salicyl occurred at the end of 1 hour in both acid and alkaline mixtures, and at the end of 24 hours about 97 per cent of the ester remained unhydrolyzed in the most alkaline buffers (pH 8.4) used. Pancreatin increased

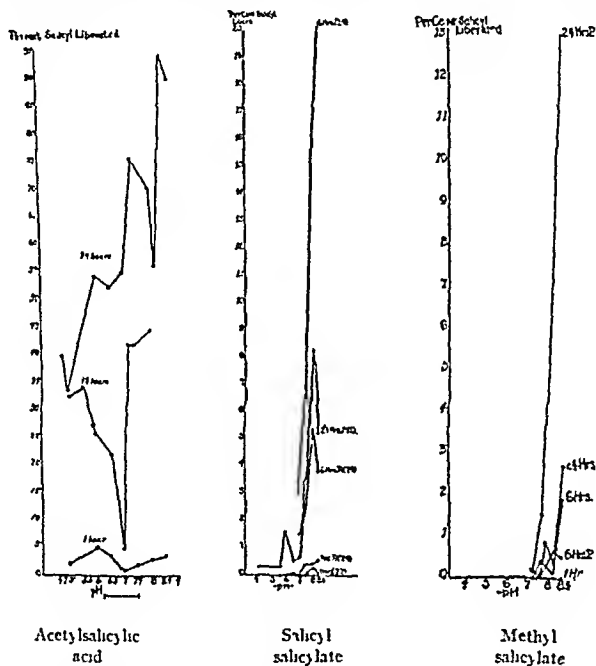


FIG. 1. HYDROLYSIS OF SALICYL DERIVATIVES IN BUFFER MIXTURES AT 38°C

P refers to pancreatin. The bracket (—) indicates the region of weakest hydrolysis of acetylsalicylic acid.

the hydrolysis at the end of 24 hours, but bile restrained it. Thus, there seems to be no doubt that salicyl salicylate and methyl salicylate undergo very limited, and acetylsalicylic somewhat more marked, hydrolysis under conditions of the alimentary tract. The presence of

food would tend to restrain the hydrolytic process, if anything, and therefore, considerable absorption of the unchanged compounds might be expected as indeed is adequately indicated by the excretory results to be described and by certain clinical claims. The curves in figure 1 illustrate the results with the salicyl derivatives tested.

Both cinchophen and neocinchophen are absorbed from the intestine as indicated by the symptomatic relief in various conditions, but nothing is known of the quantitative absorption of cinchophen, and there is some uncertainty about neocinchophen. Barbour and Lozinsky (86) studied the absorption of neocinchophen in three dogs and a patient after oral administration of the drug, which was recovered from the feces. The method was accurate to about 12 per cent with small quantities of the drug. Doses of 0.3 and 0.5 gram per kilo in dogs and the man were completely absorbed, none being recoverable from the feces. Out of 9 grams per kilo administered, only 2.7 grams per kilo were absorbed and with such large doses clumps of the drug were observed in the feces. From their results Barbour and Lozinsky concluded that the maximum limit of absorption was practically identical with the full therapeutic dose, apparently "a new and fortunate peculiarity in pharmacological behavior." The results agreed with the conclusion drawn from pharmacological evidence as to toxicity. However, the peculiar behavior of this drug is probably due to its poor solubility rather than to some providential contrivance.

*Rectal, vesical and vaginal.* Fiedler (87) found that rectal absorption of salicylate is not as good as gastric, but Massol and Minet (88) report that from 24 to 58 per cent of sodium salicylate is absorbed from the rectum. According to Heyn (89) rectal absorption is good, for salicyl appears in the urine in 15 minutes, and the iron reaction persists for from 48 to 72 hours. Absorption from the rectum is completed at the end of from 24 to 36 hours and the greatest absorption takes place during the first twelve hours as judged by ether extracts of the feces. Lenko and Kryzanowski (90) found it took 25 minutes for salicyl to appear in ureteral urine when sodium salicylate was placed into the bladder. In 1876, Fehling (91) reported absorption of salicylic acid from the vagina. Daily douches with 1:1000 to 1:600 solutions were constantly accompanied by the presence of salicyl in the urine.

Levin (67), judging from the quantity of salicyl in the blood, found

that when sodium salicylate is given intramuscularly, it is absorbed much more readily than when given by the mouth

*Permeability of colloidal membranes* According to Oswald (92), salicylic acid increases the permeability of colloids for electrolytes. This has been confirmed by Hanzlik (93) for loops of living, excised intestine. It was found that a solution of 1 per cent sodium iodide in aqueous solutions of salicylic acid (0.3 per cent), sodium salicylate (2 per cent), phenol (1 per cent), benzoic acid (saturated solution) and magnesium sulphate (5 per cent) increased the diffusion of the iodide through the wall of the excised intestine as compared with the iodide alone. Thus it is seen that the increase in permeability is not specific for the salicylate, for it occurred with an electrolyte and other substances, although the increased diffusion was most marked with the salicylate. The phenomenon is suggestive as a possible basis of the absorption of effusions from joints in rheumatic fever under salicylate treatment.

### *Distribution*

*Normal fluids and tissues* After its administration, salicyl has been found in nearly every secretion, fluid and organ of the body. Feser (30) found salicyl in all body fluids except milk, the feces, as a rule, being free from salicyl even after large doses. Drasche (62) was not able to detect salicyl in secretions of the mouth and bronchi. Its presence in human saliva has been reported by de Mussy (94) and Benoit (95), denied by Balz (96), Blanchuer (97) and Stockman (98). Bercke (99) observed that after administration of 1.5 to 2 grams of salicylic acid to the mother the child's urine gave a positive salicyl test in 2 hours, salicyl was also present in the mother's milk, but absent in the amniotic fluid (blood-free) from 4 patients. Zweifel (100) states that when salicylate was given to the mother from  $\frac{1}{2}$  hour to 4 hours antepartum, the placenta and blood of the cord contained the drug, but not the urine of the fetus. According to Puh (101) salicyl appeared in mother's milk in 24 to 36 hours after the administration of about 2 grams per day, the urine of the infant also gave a positive salicyl reaction. After intravenous injection of the sodium salicylate in dogs, J. Bernard and Ch. Livon (102) and Blanchier (97) detected it in the urine, saliva, bile, pancreatic juice, pericardial, synovial,

of healthy animals Their evidence cannot be regarded as conclusive, since the blood and serum contained the highest proportion of the salicyl, and this would necessarily have to be considered in connection with infected joints with serous effusions Moreover, the method used for estimating the salicyl was not quantitative The suggestion that diseased joints may have a predilection for salicyl has recently been tested by Frohlich and Singer (120) under different experimental conditions These investigators produced arthritis by local application of mustard and croton oils to the joints of rabbits, using the opposite untreated joints as controls After administration of large doses of sodium salicylate, the salicyl content of all joints freed from soft tissues was determined by the distillation-colorimetric method Under these conditions, there was no difference in salicyl content of the inflamed and normal joints; in fact, the inflamed joints of some rabbits contained no demonstrable salicyl Accordingly, Frohlich and Singer concluded against any favorable influence of diseased joints on the distribution of the drug Although in their reply Bondi and Jacoby (121) do not accept the work of Frohlich and Singer, claiming quite justifiably that the conditions of the two sets of experiments are not comparable, there is no doubt at least that Frohlich and Singer worked with diseased (inflamed) joints and that much cannot be said of the systemically infected animals of Bondi and Jacoby Bondi and Jacoby's criticism of the time of bleeding in Frohlich and Singer's experiments does not seem valid, since the control and inflamed joints were obtained and analyzed at the same time A safer way of testing the selective distribution of salicyl in joints would be to compare the salicyl content of the blood and joint fluid of the same individual This was done by Scott, Thoburn and Hanzlik (122) on patients suffering with rheumatic fever and receiving full therapeutic doses of sodium salicylate The salicyl content of both fluids did not differ markedly, being somewhat less in the joint fluid as might be expected A concentration of 0.02 per cent was found in blood and 0.018 per cent, in joint fluid Hence, for all practical purposes, the alleged selectivity of salicyl for inflamed joints does not exist If anything, the results of Frohlich and Singer and of Scott, Thoburn and Hanzlik suggest that the swollen and inflamed membranes of the synovia act as barriers to the diffusion of the salicylate

*Concentration in the blood of rheumatic and normal individuals*

This is somewhat less in the blood of rheumatic than of normal individuals. Using full therapeutic doses of sodium salicylate by mouth equivalent to about 13 grams expressed as salicylic acid, Scott, Thoburn and Hanzlik (122) found that the concentration in normal individuals ranged from 0.018 to 0.035 per cent, average 0.0265 per cent, while in rheumatic fever patients it ranged from 0.014 to 0.031 per cent, average 0.021 per cent. The theoretical concentration estimated was 0.02 per cent which compared favorably with the concentration found in rheumatic patients. Probably the lower concentration found in rheumatic individuals was due to some destruction of the salicyl to be discussed under "excretion." After the administration of 1 gram sodium salicylate to a normal person, Giessinger and Debray (123) report the following percentage concentrations in serum, 0.004 to 0.005 at the end of 10 minutes, 0.05 to 0.006 at the end of 30 minutes, 0.01 at the end of one and one-half hours, and 0.001 per cent at the end of 18 hours. Administration of the drug in capsules did not change the results.

*Binding power of the blood for salicylic acid* This has been studied recently by means of extraction and dialysis experiments, and the results seem to indicate some binding of salicyl by blood proteins, varying somewhat with the source and condition of the blood, as in allergy. Van Leeuwen and Drzimal (124) found that the addition of 0.01 gram of salicylic acid to 10 cc. of defibrinated beef blood yielded no ether extractable salicyl, but with 0.015 gram, 0.03 mgm. was extracted and with 0.02 gram, 1 mgm. Normal human blood gave the same results except that the extraction limit was lower (average) with 0.01 gram added to 10 cc. blood, while the blood of asthmatics tested for hypersensitivity to acetylsalicylic acid gave regularly a still lower extraction limit, that is, about 4 mgm. to 10 cc. of blood. From dialysis experiments, it was shown that salicylic acid in serum dialyzed less completely than from water or Tyrode's solution. The quantity held back by normal and asthmatic serums was from 0.072 to 0.9 mgm. in 5 cc. serum while serums of asthmatics hypersensitive to acetylsalicylic acid held back much less, the figures, however, not being given. Seventy-eight hundredths of a milligram was bound by 5 cc. of beef serum and 1.08 mgm. by serum of normal persons and asthmatics,

and the addition of hydrochloric acid did not liberate more. It is claimed by the authors that the results indicate that in asthmatics the binding power of blood for salicylic acid is reduced and there is a higher concentration of the free drug exerting a more pronounced action than if it were bound. Moreover, they think the phenomenon is of significance for the allergic state in general. If their results were more striking and convincing, the argument might have some basis.

The peculiar binding of salicyl by blood plasma has been shown by Chabanier, Lebert and Lobo-Onell (125) in another way. Using collodion sacs, they observed a rapid and almost complete disappearance of salicyl from 0.9 per cent sodium chloride dialyzed against plasma, while only a very small proportion of the salicyl dialyzed from salicylated plasma into untreated plasma. Furthermore, when 10 cc of serum containing 0.01 per cent sodium salicylate was dialyzed against 0.9 per cent sodium chloride containing the same concentration (0.01 per cent) of salicylate, the sodium chloride-salicylate mixture was found to contain only a trace of salicyl at the end of 180 to 300 minutes. The dialysis into serum was greater the greater the volume of serum. In other words, the serum attracted salicyl despite the original equal content. No attention was paid to the pH in these experiments, a factor that could conceivably affect the result. In later experiments, the same authors (126) claim to have demonstrated further that salicyl is adsorbed by the blood proteins and that its excretion is independent of any renal threshold. On the other hand, Coquonin (127) found that dialyzing salicylated serum against physiological salt solution free from salicyl, or containing the same concentration as the serum, gave an even distribution of the salicyl after sufficient time. Friedrichsen (128) demonstrated a difference in the distribution of salicyl between the corpuscles and serum in beef and rabbit blood. Working with quantities of 0.2 to 0.6 gram salicylate he found a higher concentration, i.e., 1.2 per cent, in serum than in the corpuscles, i.e., 1.0 per cent, a difference that might explain the results in the bloods of van Leeuwen and Drzimal, for probably the condition of the corpuscles *in vitro* has some influence on their binding power with salicylic acid, which in turn would influence the results of extraction and dialysis. In any case the results

of these dialysis and extraction experiments do not settle the question of the form in which salicyl exists in the circulating blood after administration

*Form in which salicylates exist in body fluids* From the modern conceptions of the reaction of body fluids, it would appear quite probable that the salicylates circulate as the sodium salts. This was thought to be the case by Salkowski (43) and by Meyer and Kolbe (33) as early as 1875. Meyer and Kolbe thought that salicylic acid, when taken internally, was neutralized by the alkaline phosphate and other alkalies of the tissues. Two hundred cubic centimeters of fresh dog's blood was found by them to "bind" chemically about  $\frac{3}{4}$  gram of salicylic acid. Taken by mouth, the salicylic acid is first neutralized by the alkaline juices of the intestine and, therefore, is absorbed chiefly as the sodium salicylate. However, it was claimed by Binz (52) in 1876 that the high tension of carbon dioxide of the blood and other fluids in rheumatic fever liberated free salicylic acid which, he believed, was responsible for the therapeutic benefits. The evidences from experiments in vitro offered by him were as follows. Carbon dioxide shaken with a 1 per cent solution of sodium salicylate gave up to ether a substance which gave a positive salicyl test with iron. Urine containing sodium salicylate and free carbon dioxide did not putrefy as readily as when it contained either salicylate or carbon dioxide alone. Salicylic acid crystals were present in two specimens of highly acid urine. It was argued by him that lactic and other fatty acids assisted in the liberation of salicylic acid. From later experiments, Binz (129) concluded that sodium salicylate acts as an energetic bactericide and is destructive when an alkaline bacterial medium is impregnated with as much carbon dioxide as corresponds to that of inflamed tissues in man. The experiments were performed as follows. Under a pressure of half an atmosphere of carbon dioxide about 20 per cent of the gas was dissolved in an alkaline mixture, consisting of sugar, potassium phosphate, ammonium tartrate, and 0.5 per cent of sodium salicylate, and infected with bacteria. This remained sterile for four months at summer and room temperatures. The same experiment performed without salicylate showed an extensive bacterial growth in one week. When the experiment was performed with salicylate, but without carbon dioxide, putrefaction and bacterial



growth occurred in a few days. When the mixture (containing salicylate) was impregnated with about 20 per cent of air, or if the whole was exposed to air without pressure, turbidity and putrefaction resulted in both cases.

Kohler (130) observed that when salicylic acid was dissolved in normal blood, no salicyl was given up to ether, but when blood of asphyxia was used the ether extract contained salicyl. From experiments on animals, Kohler concluded that salicylic acid existed in the blood as sodium salicylate, but that in death from salicylate poisoning the carbon dioxide content of the asphyxial blood was sufficiently high to liberate free salicylic acid, because such blood gave up salicyl to ether without the further addition of acid.

The carbon dioxide (and other acids) theory was strongly opposed by Feser and Friedberger (131) on the ground that drawn blood containing salicylate would not yield any of it to ether until further acidified. These observers advanced the theory that salicylic acid exists as an albuminate in the blood. However, according to Fleischer (132), who also held the opinion that salicylic acid as such does not exist in the blood, even combination with proteins is improbable, since the digestion of blood with salicylic acid resulted in a precipitate and the filtrate contained practically all of the salicylic acid. By digesting salicylic acid with proteins, i.e., albumin, casein and syntonin, or fibrin, and after shaking out the digested mixture with ether, and treatment with boiling water, Farsky (133) found that a residue remained which contained 14.2 per cent of salicylic acid, and the formula  $C_{72}H_{112}N_{18}SO_{22}$  was assigned to it. It was found to be soluble in gastric juice with liberation of salicylic acid. Marmé (134) produced fever in a dog and administered sodium salicylate. The venous blood was then extracted with ether, but no trace of free salicylic acid was found.

Still another view was advanced by Jacoby (135). Jacoby believed that salicylate in the blood serum of injected animals existed in a different form than when salicylate was added directly to serum outside the body. The view was based on the following evidence. The blood serum of rabbits previously injected with sodium salicylate yielded salicylate containing precipitates with ammonium sulphate, but the addition of salicylate to serum gave precipitates free from

salicylate In short, salicylate in the circulating blood seemed to be attached to the proteins Jacoby suggested that the salicylate may be bound in some way with amino compounds, or proteins resembling them, in the intestine

The question of the form in which salicyl exists in the circulating fluids and the tissues of the body touches on an important point, namely, the mechanism of the action of salicylates in acute articular rheumatism The etiology of rheumatic fever is not absolutely settled, but assuming that the condition is a bacterial infection, and since salicylic acid is more bactericidal than sodium salicylate, and from the fact that carbon dioxide can liberate the acid from sodium salicyl-

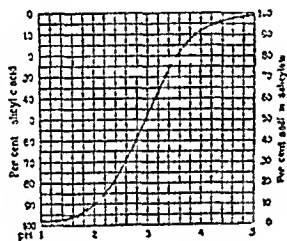


FIG 2 LIBERATION OF SALICYLIC ACID FROM SODIUM SALICYLATE ACCORDING TO HYDROGEN ION CONCENTRATION (pH) OF THE SOLUTION AT 40°C, AFTER BOOTS AND CULLEN (138)

ate, it is suggestive at least that salicylate might exert its beneficial action by virtue of the free salicylic acid in the inflamed tissues where the carbon dioxide tension may be very high According to Ewald (136), the normal carbon dioxide tension of tissues is 6 per cent, but in inflamed tissues it may reach 20 per cent, and may be 5 to 7 per cent higher in inflammations than in asphyxias Unfortunately, however, the tests of the acid theory that have been made have yielded only negative results For instance, Hanzlik (137) found that definite liberation of free salicylic acid from sodium salicylate in pure buffer solutions required a hydrogen ion concentration equivalent to a pH of 6.5, and that the presence of 25 per cent serum or plasma protein required a much higher degree of acidity, namely a pH of 5.9, both being

degrees of acidity incompatible with, and indicating the improbability of demonstrating free salicylic acid in the blood during life. This was fully confirmed on animals subjected to fatal asphyxia and whose cardiac and arterial bloods became slightly acid (pH 6.8). Extracts of salicyl-containing fluids from inflamed joints of rheumatic patients were found by Scott, Thoburn and Hanzlik (122) not to contain free salicylic acid. This might be expected, for joint fluids of rheumatic fever are probably usually alkaline, as indicated by the results of Boots and Cullen (138), who found values of from pH 7.27 to 7.42 for sixteen joint exudates. Consequently, the theory that free salicylic acid, liberated by virtue of the greater carbon dioxide content of inflamed tissues and their fluids seems untenable. The results discussed above dispose also of another theory, suggested by Poulsson (139), namely, that the absence of a right-sided valvular (tricuspid) endocarditis is due to the antiseptic qualities of free salicylic acid liberated here by virtue of the greater carbon dioxide content of the venous blood. The liberation of salicylic acid from sodium salicylate according to the hydrogen ion concentration (pH) of the solution at 40°C is shown in figure 2.

Since the esters of salicylic acid are only partly hydrolyzed before absorption takes place, a considerable proportion of the unchanged compounds appears in the circulation and tissues (21, 23, 24). The acetylsalicylic acid appears as the sodium salt and possibly also the salicyl salicylate, but the methyl salicylate appears as such. This is probably the reason for the differences in pharmacological action and clinical toxicity of these compounds from those of ordinary salicylate. This is contrary to the current conceptions of the fate of acetylsalicylic acid, which was claimed by Gazert (140) among others to be decomposed almost entirely in the intestine, and its action, dependent on the liberated salicylate. The results of Hanzlik and Prescho (21) on the decomposition of acetylsalicylic acid in alkaline and acid buffer solutions agree with those of Chistoni and Lapresa (141) who observed decomposition of the drug not only in alkaline juices, but also in gastric juice. These results are against the claims that acetylsalicylic acid is non-irritating in the stomach. Bondi and Katz (142) found that acetylsalicylic acid is absorbed in part as such from the intestine, though all is decomposed before excretion. These

observers also noted that strong trypsin preparations with the addition of bile decomposed this acid in five hours at 37°C to the extent of 50 per cent, minced liver containing 1 per cent sodium bicarbonate accelerated the decomposition as compared with liver alone Hanzlik and Presho (23, 24) observed no decomposing influence of bile and pancreatin on salicyl salicylate, and only some increase in decomposition of methyl salicylate on incubation with pancreatin According to Gillippi (143), novaspirin and benzosalin are partly decomposed by living tissues and their ferments However, benzosalin is expelled with the feces mostly unchanged

### *Excretion and fate*

*General* Salicylates are excreted in the urine mainly as such, and apparently to a small, though variable, extent as salicyluric acid and a number of other products On account of their rapid absorption, the feces, as a rule, contain exceedingly small amounts, if any at all The presence of salicyl ethereal sulphate, salicylglycuronic and oxysalicylic acid in urine has been reported by C Neuberg (144), ur-salicylic acid by Baldoni (145) According to Nencki (146) saligenin (salicyl alcohol) in the body is converted into and appears as salicylic and salicyluric acids

Sometimes the color of urine is rendered green after salicylate administration Wolffberg (147) thought this to be due to a decomposition product of indican, which was increased Fleischer (148) considered the greenish brown color to be due to alkaptone formation rather than to change in indican or to pyrocatechin formation Robin (149) regarded it as due merely to increased excretion of indican, G Sée (150) as due to the formation of pyrocatechin from salicylate

Urine containing salicylate reduces Fehling's solution This was first observed by Fleischer (148), then by Smith-Pye (151) and later confirmed by Pollnitzschek (152)

The rate of excretion of salicylate varies with the dosage and diuresis Drasch (62) found salicyl in the urine within a few minutes after administration of 0.01 gram by mouth, after 0.01 gram the urinary reaction was still present after 24 hours After ordinary therapeutic doses the reaction did not disappear until at the end of five days Large doses were necessary by subcutaneous injection to bring

about similar urinary reactions Balz (96) had the unusual opportunity to study the excretion in urine from the ureters of a patient with epispadias and defective anterior bladder wall so that catheters could be easily inserted into the exposed orifices of the ureters After oral administration of sodium salicylate, the time of appearance of salicyl in urine was  $8\frac{1}{2}$  minutes, of salicylic acid in 20 minutes, but unfortunately no statement is made as to the acidity of the urine, nor is the extraction method fully described An increase in diuresis was also observed

*Duration of excretion* According to Geissler (153), complete elimination may take place in 12 hours, but ordinarily it lasts 24 to 48 hours, as observed by G Sée After doses of 1 to 2 grams of the salicylate, Blanchier (97) found excretion to be completed in 22 hours, after 4 to 5 grams at the end of 44 hours In rheumatic individuals receiving 4 to 8 grams, traces were found in urine at the end of 72 hours Herbivora excrete salicylate more rapidly than carnivora, as observed by Feser and Friedberger, quoted by Blanchier (97), and for this reason endure much larger doses. Blanchier stated that the time of appearance in urine is about 12 minutes after administration, in bile 30 minutes, and in saliva 45 minutes Cornet (154) observed the appearance of salicyl in urine in  $\frac{1}{2}$  to  $\frac{3}{4}$  of an hour after administration of salol and the reaction was still present at the end of 46 hours A diminution and prolongation in the excretion of salicylate has been observed in disease of the kidney and circulatory organs by Chelchowski (155) and Purpus (156) Brouardel (157) claimed the time of appearance in urine in older individuals was longer (2 hours) than in the young (15 minutes), and lasted longer in the old (2 to 8 days) than in the young (24 hours). However, Ehrmann (158) found excretion to last from 36 to 48 hours in normal individuals, and thus was not different in rheumatism. The administration of alkali was thought to hasten the excretion After the cutaneous application of salves, Schumacher (66) found the excretion to last 2 days According to Herissey, Friesinger and Debray (159), 0.002 gram sodium salicylate by mouth just gives a positive iron salicyl reaction in urine, and after a dose of 0.2 gram the reaction lasts 6 hours

The excretion of salicyl in urine after the administration of acetylsalicylic acid and novaspirin was found by Block (160) to begin in

about  $\frac{1}{2}$  hour and last 2 days. It was also reported by Fillippi (108) that the excretion of salicyl in the synovia and urine of rabbits after administration of acetylsalicylic acid was slower than after sodium salicylate. After taking 1 gram of sodium acetylsalicylate, Dreser (11) reported that excretion of salicyl was completed at the end of 12 hours. The observations of Pinczower (80) indicated that the appearance of salicyl in urine after salicylic acid, sodium salicylate, acetylsalicylic acid, novaspirin, salol, salpyrin and benzosalin presented no striking differences. According to Rocco (161) excretion of salicyl salicylate lasted 22 hours with rabbits and 73 hours with dogs.

After full therapeutic doses and under controlled conditions, the differences between different salicyl compounds as to duration of excretion is more strikingly demonstrated. Hanzlik, Scott and Thoburn (162) and Hanzlik, Scott and Reycraft (163) observed a median duration of 78 hours in normal subjects, of 72 hours in rheumatic patients, and of 80 hours in patients with miscellaneous conditions. After acetylsalicylic acid in convalescent and rheumatic patients, Hanzlik and Prescho (21) found the duration to be a median of 114 hours, after salicyl salicylate in convalescents, a median of 101 hours, and after doses of 1 gram each in 3 normal subjects, a median of 48 hours (23). With methyl salicylate in convalescents, the duration of excretion was a median of 96 hours, and after 1.18 gram doses in 3 normal subjects, 55 hours (24). In 4 dogs and 1 cat receiving a median dosage of 0.2 gram per kilo of methyl salicylate gastrically and intramuscularly, the median duration of salicyl excretion observed by Hanzlik and Wetzel (164) was 96 hours. It is obvious, therefore, that the salicyl derivatives require a much longer time for completion of excretion than sodium salicylate, despite the larger, absolute dosage of the latter. Even the smaller (1 gram) doses of the derivatives seem to indicate a tendency to retention. The tendency to longer retention in the body may be one factor among others in the greater toxicity and pharmacologic activity of certain of the derivatives. A summary of the results on duration of excretion of the different salicylates is presented in table 1, which contains the main results of our excretory studies.

*Quantitative methods of studying excretion.* Feser and Friedberger (131) were the first, in 1875, to study the quantitative excretion of

TABLE 1

*Summary of urinary excretion of different salicylates in normal individuals, in rheumatic fever and other diseased conditions and in animals after full and small therapeutic doses*

COMPOUND	NUMBER OF DIFFERENT INDIVIDUALS	DIAGNOSIS	MEDIAN TOTAL DOSE ADMINISTERED	MEDIAN DURATION OF EXCRETION	MEDIAN TOTAL SALICYL EXCRETED	MEDIAN TOTAL UNCHANGED DISSOLVABLE EXCRETED (RANGE IN PARTNERS)
			grams	hours	per cent	per cent
Sodium salicylate	11	Normal	14.6	78*	79.7	
	8	Rheumatic fever	16.0	72†	60.4	
	6	Miscellaneous diseases‡	11.6	80	57.8	
	9	Animals (8 dogs and 1 cat)	1.57§		56.6	
Acetylsalicylic acid	4	Convalescents	7.0	117	80.0	22.7 (10.5-36.6)
	3	Rheumatic fever	12.0	114	68.5	33.4 (21.4-41.1)
Salicyl salicylate	4	Convalescents	8.5	101	63.0	6.2 (6.1-17.6)
	3	Normal	1.0	48	66.0	
Methyl salicylate	7	Convalescents	7.96	96	50.8	0.098** (0.055-0.116)
	3	Normal	1.18	55	50.5	
	5	Animals (4 dogs and 1 cat)	1.54††	96	25.9	0.36†† (0.2-0.52)

\* Accurate data from 6 subjects

† Accurate data from 6 patients.

‡ Chronic nephritis, chronic alcoholism and morphinism, tuberculosis with fever, Basedow's disease

§ 0.2 gram per kilo gastrically, intramuscularly and hypodermically

\*\* Approximate from 5 subjects

†† 0.22 gram per kilo gastrically.

†† 1.4 per cent.

salicyl in urine The salicylic acid was recovered by extraction of the urine with ether These authors recovered 63 per cent of the quantity administered, and drew the conclusion that the rest of the salicylic acid was destroyed in the organism, since it was not excreted by the feces This was claimed to be incorrect by U Mosso (165) because Feser and Friedberger did not consider the presence of salicyluric acid Mosso claimed that salicyluric acid is only partly soluble in ordinary ether, but much more soluble in ethyl acetate, so that with a mixture of ether and ethyl acetate both the salicylic and salicyluric acids could be completely extracted Since the results of Mosso have been frequently quoted without sufficient appreciation of the difficulties of the method used, a short description of the procedure will be given here

In detail the quantitative separation, as carried out by Mosso, consists in first removing the mucoid and other substances by precipitation of the urine with neutral lead acetate, the precipitate is removed and washed salicyl-free Then the filtrate is treated with ammonia and lead acetate and heated The precipitate, which now contains the salicylates is removed on a filter paper and decomposed with ammonium carbonate or sulphuric acid, filtered, and the precipitate washed until salicyl-free From the filtrate the salicylic acids are now removed by repeated extraction with small quantities of a mixture of ether and ethyl acetate This requires about 6 to 8 extractions The ethers are allowed to evaporate spontaneously from a suitable dish and the crystalline residue remaining is weighed The whole is then heated on a water-bath until the weight becomes constant, it is weighed again, and the weight of this second residue corresponds to salicyluric acid The difference between the weights of the two residues corresponds to salicylic acid which had volatilized Mosso collected urine for from 2 to 3 days, and recovered 96.8, 98.5, 102.1 and 106.7 per cent of the total salicylate administered His conclusion was that salicylic acid is not decomposed in its passage through the body It is not certain if Mosso made complete collections of urine or not The application of Mosso's method by Thoburn and Hanzlik (166) to complete collections of three urines gave recoveries of 126.14, 215 and 223 per cent, and the salicyluric portions from eight animal and human urines were unobtainable Hence, it was concluded that the method



was not suitable for quantitative estimations of salicyl. This was also the conclusion with respect to a number of other methods depending on extraction of salicyl by immiscible solvents directly from, or its direct colorimetric estimation in, urine.

The governing principle of a good method is the recovery of the total salicyl in pure form, or in aqueous solution free from any disturbing elements, before it can be estimated quantitatively. The estimation can then be easily and accurately made by the color reaction with iron (ferric). The method described by Thoburn and Hanzlik (166) meets all the requirements for urine and other body fluids. Applied to urine, it consists briefly of the hydrolysis of an aliquot portion of the specimen with 85 per cent phosphoric acid, distillation with the aid of steam until all the salicyl is driven off, and colorimetric estimation of the distillate with ferric alum. For details and its application to other body fluids the original should be consulted. The method has been used successfully by a number of investigators and applied by many trained and untrained workers to hundreds of urines and body fluids in our studies during the past ten years. The method has been frequently controlled in published and unpublished experiments with extraction methods in which different immiscible solvents were used and the residual urines treated in various ways for the detection of any unremoved salicyl. The acid residues left after the distillation of 20 different urinary specimens have been repeatedly shaken out with ether, ethyl acetate, chloroform and benzene, and in no single instance was there a positive iron test for salicyl obtained from such extracts. The agreement in the majority of instances has been as good as could be expected, and in many cases the quantities of salicyl recovered have checked nearly perfectly. This is well illustrated by the excretory results in the studies of Hanzlik and Presho (21, 23, 24) on acetylsalicylic acid, salicyl salicylate and methyl salicylate. In other words, the hydrolysis-distillation method recovers all the salicyl excreted in urine, the recent claim of Holmes (167) to the contrary notwithstanding. Holmes' results with his modification of the hydrolysis-distillation method are not altogether satisfactory. Furthermore, he has overlooked five other publications by Hanzlik and associates, besides the one criticized by him, dealing with excretion of salicyl under a variety of conditions, in which high and low

recoveries have been obtained. Recently again, as on many occasions in the past, some high urinary recoveries of 95 to 98 per cent of the salicyl administered have been obtained in this laboratory with the original distillation-hydrolysis method. This, however, is not invariably true, since the total quantity excreted varies with the individual and the condition. We may now consider the quantitative excretion of the different salicyl compounds. A convenient summary of the principal results is presented in table 1.

*Excretion of salicyl by normal and rheumatic individuals.* Salicyl is incompletely excreted, a part being destroyed in the tissues. The administration of daily doses of from 0.21 to 2 grams of salicylic acid for several days to 12 normal subjects resulted in a recovery of 46.8 per cent of total salicylates in the urine (Wiley (168)). Wiley considered the remainder to be changed to salicyluric acid or stored in the body, but it appears that the quantitative method used for the estimation of salicyl was faulty. The high recoveries of Mosso (165) were mentioned above, but the method used was also unsatisfactory. Baldoni (169), who claimed that the data of Mosso and others on elimination were discordant, recovered a total of about 86 per cent with his method depending on immiscible solvents. Using full therapeutic doses of sodium salicylate, that is, about 15 grams, Hanzlik, Scott and Thoburn (162) and Hanzlik and Wetzel (26) found that about 75 to 80 per cent of the total administered was excreted in urine. Since the loss could not be accounted for in sweat and feces or by retention, it was concluded that about 20 per cent of the salicyl was destroyed in its passage through the body. After administration of one gram doses to eight human subjects and making complete collections of urines, Devrient (170) recovered only from 1.01 to 14.68 per cent in urine and concluded that the remainder was destroyed or adsorbed in the body. He denies the claims of Mosso (165) and Bondzynski (82) that excretion is complete, and also the claim of Brouardel (157) that age affects excretion, since young and old subjects excreted about the same quantities in his experiments. With his sulphuric acid-hydrolysis-distillation method, Holmes (167) claims to recover usually over 90 per cent of the total (2 to 5 grams) sodium salicylate administered, but his lower recoveries of from 70 to 80 per cent are left unexplained. After taking 1.5 and 2 grams of salicyluric acid, about

84 and 85.7 per cent were recovered. On the whole, therefore, the percentage recoveries of this author, with the alleged improvement in method, are no better than those of previous investigators and the limited number of his experiments does not settle the question of destruction.

In rheumatic fever, Hanzlik, Scott and Thoburn (162) found the total excretion was only 60 per cent, that is, about 15 to 20 per cent less than in normal individuals. This difference was greatest in the early periods, i.e., during the first ten to twenty hours after administration of the drug. The concentration of salicyl in the blood and urine of rheumatic patients at "toxicity" was also less than in normal individuals. The differences were not due to diuresis, nor to retention and vicarious excretion of the salicyl. They seemed to be due to increased destruction of the salicyl in the febrile rheumatic organism.

*Excretion in other fevers and disease conditions* A markedly diminished excretion was found by Hanzlik and Wetzel (26) in patients with febrile tuberculosis and syphilis and with Basedow's disease, in drug habitués (chronic alcoholism and morphinism) and in nephritis of both man and dog. The loss of salicyl, amounting to about 40 per cent, was attributed to increased capacity for destruction due to the increase in metabolism (katabolism) in the febrile conditions and Basedow's disease, and to retention with prolonged exposure to the destructive action of the tissues in nephritis.

*Bicarbonate on excretion* Fleischer (148) claimed that the administration of sodium bicarbonate shortened the period of elimination of salicyl from 36 to 14 hours. Ehrmann (158) also claimed that alkali hastened the excretion, but Hanzlik, Scott and Thoburn (162) and Hanzlik, Scott and Reycraft (163) were unable to confirm these claims in patients receiving full therapeutic doses of sodium salicylate and doses of bicarbonate up to 16 grams. In the majority of patients the dosage of salicylate and bicarbonate was equal and the urines were definitely alkaline in all, but without demonstrable influence on the duration and percentage of excretion.

*Excretion of esters and other derivatives* These are excreted partly unchanged and partly as ordinary salicylate, the total excretion being generally less than after the administration of sodium salicylate. Baas (84) found that the salicyl excreted after ethyl salicylate corre-

sponded only to 21 per cent of the ester given, with methyl salicylate only about 24 per cent. Baas concluded that these esters were only partially hydrolyzed in the intestine, a part remaining unabsorbed, and in part the esters were excreted combined with ethereal sulphates. Old urine possessed the odors of these esters, since their ethereal sulphate compounds had broken down and liberated the esters. Salicylamid was found to behave similarly, but salol was found to be entirely decomposed. After the application of 2 grains of methyl salicylate to the skin, Linnoisier and Lannois (68) found 10 per cent of the salicyl in the urine in 24 hours, after 4 grains, 25 to 30 per cent. After internal administration of ethyl salicylate, Bondzynski (82) claimed 91.3 per cent of salicyl in the urine, no ester was found in the feces.

Using full therapeutic doses, Hanzlik and Presko (21, 23, 24) made a systematic study of the urinary excretion of acetylsalicylic acid, salicyl salicylate and methyl salicylate. The results were checked by two quantitative methods, that is, by hydrolysis-distillation and by a special extraction technique in which the residual urines were treated for any unextracted salicyl so that all the salicyl reacting with iron, which includes salicyluric acid, was removed. From 4 to 14.8 grams of acetylsalicylic acid were administered to 6 subjects of whom 4 were convalescents and 2 suffered with rheumatic fever. The results of uncomplicated experiments were as follows: a total salicyl excretion of about 80 per cent in the convalescents and 68.5 per cent in the rheumatics, a difference that agreed quite well with that observed with sodium salicylate. From 8.8 to 36.6 per cent of the acetylsalicylic acid administered was excreted unchanged, and this was not influenced by the clinical condition, dosage of the drug, diuresis, total salicyl excreted and some other factors. The excretion of unchanged acetylsalicylic acid was anticipated from the results of hydrolysis experiments *in vitro* discussed in the section on absorption. After 2 gram doses in patients, Devrient (170) recovered 3.6 and 2.25 per cent of the unchanged acetylsalicylic acid in urine, and after 1 gram magnesium acetylsalicylate, 2.8 per cent. Using a method similar in principle to that of Hanzlik and Presko, Chistoni (171) recovered about 33 per cent of unchanged acetylsalicylic acid after 1 gram doses of the drug in human subjects.

Doses of from 4 to 12 grams of salicyl salicylate in 4 convalescent

subjects yielded a total salicyl excretion of 63 per cent, and of 66 per cent in 3 normal subjects, receiving 1 gram doses of the drug (Hanzlik and Prescho (23)) In the 4 subjects receiving the high doses, about 6 per cent of the total salicyl salicylate administered appeared unchanged in the urine This result was partly predicted from the hydrolysis experiments *in vitro*, since these suggested that the conditions in the alimentary tract would permit only a limited decomposition of the drug The results on the recovery of total salicyl agreed with those of Baldoni (169) who recovered an average of 65 per cent in 3 subjects

In 6 convalescent patients, who received from 6.58 to 10.72 grams of methyl salicylate, the excretion of total salicylate was rather variable, the median being 50.8 per cent, uninfluenced by dosage, diuresis and clinical condition Three normal subjects receiving 1.18 grams each of the methyl salicylate showed a total salicyl excretion of about 50.5 per cent (median) The excretion of the ester in 3 patients was from 0.055 to 0.116 per cent of the total administered This was much less than could be predicted from *in vitro* experiments on hydrolysis which was very small under the most favorable conditions Hence, it seemed that the alkalinity, enzymes and bile of the alimentary tract did not participate much in the considerable liberation of sodium salicylate from the ester in its passage through the body Apparently the greater part of the methyl salicylate was hydrolyzed in the tissues The percentage excretion of methyl salicylate in human subjects was less than that found by Hanzlik and Wetzel (164) in animals which excreted from 0.2 to 0.52 per cent of the total administered (0.22 gram per kilo) gastrically The greater variability of excretion of methyl salicylate as compared with salicyl salicylate and acetylsalicylic acid may be due to slower and irregular absorption suggested in the experiments However, this does not account for the incompleteness of its excretion

Although the excretion in feces was not studied with any of these derivatives, it appears improbable that expulsion with the feces, or incomplete absorption, would account for the losses, since the total excretions after small doses (around 1 gram) of salicyl salicylate and methyl salicylate were about the same as after the large or full therapeutic doses Finally, complete collections of urines were made in all

cases, that is, until they were salicyl-free. Therefore, the loss of total salicyl after these derivatives, as also after sodium salicylate, seems best accounted for by destruction of the salicyl group in the tissues.

*Excretion in animals* This is generally less after sodium salicylate, but more after methyl salicylate than in man, while after acetylsalicylic acid the excretion is about the same. Hanzlik and Wetzel (26) found the total excretion of sodium salicylate in 8 healthy dogs and 1 cat receiving about 0.2 gram per kilo gastrically, intramuscularly and hypodermically to be a median of 56.6 per cent, and this remained practically unaltered in 2 dogs whose livers were degenerated by treatment with phosphorus, and in 2 dogs and 1 cat receiving powdered thyroid with the idea of increasing the destruction. The excretion in normal animals, individually and collectively, was much less than in normal human subjects, and is indicative of a greater capacity for destruction. In a dog with experimental nephritis from salicylate itself, the total excretion was reduced to 26.6 per cent and this was in line with the small excretions of patients with nephritis. As for acetylsalicylic acid, Pitini (172) administered 1 and 1.5 gram doses to 6 dogs and recovered from 19 to 33 per cent of the total salicyl excreted as the unchanged drug, which is about the same as in the human subjects of Hanzlik and Prescho (21). Methyl salicylate was mentioned above.

*Destruction under biological conditions* The excretory results discussed above point to some destruction of the salicyl group in its passage through the body. There are other evidences which indicate the relative ease with which salicyl is decomposed by living organisms. It is a familiar fact, though formerly insufficiently appreciated, that solutions of sodium salicylate and other salicyl compounds gradually lose strength on standing. This is easily demonstrated in weak solutions of salicylate used as standards in quantitative estimations. Such solutions do not retain their original strength for more than about two weeks. The deterioration is due to some form of living matter such as fungi, since solutions containing a preservative (chloroform) and free from fungi do not deteriorate. This evidence was obtained in an extensive study of the destruction by Hanzlik and Wetzel (26), who observed, in addition, that destruction of the sali-

cylate occurred by yeast, though somewhat less than by the fungus growing naturally in salicylate solutions, and by hashed organs of animals. The destruction did not appear to be the special function of a particular organ, such as the liver, since the excretion in certain diseases of the liver in man and in hepatic degeneration in animals was within the normal range. Finally, the destruction was found to be greater in fever, Basedow's disease and nephritis, that is, during increased katabolism and in retention, than in normal subjects. It was also greater in animals than in man. Devrient (170) could recover only from 4.5 to 16 per cent from hashed organs, but some adsorption could not be eliminated, since the addition of salicylate to gelatin did not permit complete recovery, that is, at most 44 per cent. Taken as a whole, therefore, the evidence brought forward would seem to leave no doubt concerning the destruction of the salicyl group by living organisms. The destruction appears to be a part of the general function of metabolism. This view is contrary to the older views of Nencki (146) and Mosso (165) whose work, however, can not be accepted without question. It is consistent with the familiar chemical fact that salicylate when heated with alkalis is rather readily changed to phenol. The destruction of salicyl by living organisms should be of some practical interest in the metabolism of phenols and other aromatic derivatives. It may help to appreciate why salicyl in low concentrations is not an effective antiseptic in the blood and tissues, the necessity of using large doses to secure therapeutic effects, its harmlessness when used in low concentrations as food preservative, reference, of course, not being made to free salicylic acid and its local effects.

*Salicyluric acid* The existence of this elusive product in the body has been denied and affirmed from time to time since the first report of its occurrence in urine by Bertagnini in 1856 (173). Bertagnini obtained a crystalline residue by ether extraction which, when exposed to a current of air at 140° to 150°C, yielded two products. That which volatilized was declared to be salicylic acid and the remaining non-volatile portion, salicyluric acid, because when purified it possessed the following properties: melting point 160°C, it was readily soluble in ethyl acetate and alcohol, but less so in ether, more soluble in hot water, but almost insoluble in cold water, the taste was bitter, and it

possessed an acid reaction. The elemental composition, including nitrogen, answered the theoretical one for salicyluric acid and the empirical formula was given as  $C_{21}H_{22}N_2O_9$ . From the following formula usually given for it,  $C_6H_4(OH)(CO-NHCH_2COOH)$ , it is seen that it is a conjugation product of salicylic acid with glycocholic acid, and, therefore, chemically analogous to hippuric acid ( $C_6H_4(CO-NH-CH_2COOH)$ ). Its chemical properties resemble those of salicylic acid and it gives the characteristic pink to violet reaction with iron. Accordingly, any method depending on the iron reaction for the estimation of total salicyl directly in solution or extractives must include salicyluric acid. For over 60 years after Bertagnini, nearly all investigators followed essentially the same procedure, except for minor modifications, in the isolation of salicyluric acid as employed by Bertagnini, with variable successes. A brief résumé of these later researches follows mainly to illustrate their uncritical nature.

In a report by Gnehm (174) to the Swiss Chemical Society in 1875, it is stated that Piccard was able to confirm the results of Bertagnini, although he objected to the method of purification (by means of sublimation) recommended by Bertagnini as insufficient to give pure salicyluric acid. No data are presented, but according to Neubauer and Vogel (175), who quote Piccard, the separation of the two acids, i.e., salicylic and salicyluric acids, was accomplished by crystallization from ether and benzene, the salicylic acid crystallizing first. According to Stockman (176), salicyluric acid is insoluble in boiling benzene, and according to Baldoni (169), in chloroform. These solvents were used by these investigators to separate salicylic from salicyluric acid in urinary residues obtained by ethereal extraction. However, in neither case were the products sufficiently studied so as to identify them as salicyluric acid. In some earlier work, Baldoni (177) determined the melting point of salicyluric acid as  $178^\circ\text{C}$ . Stockman did not determine the melting point of his products, but identified them by their solubilities, by testing for ammonia (nitrogen) by soda lime and by their action on yeast and some common bacteria. Obviously such tests are not sufficiently specific and definite. According to Stockman, the urines after administration of salicin, saligenin and methyl salicylate contained salicyluric acid. U. Mosso (165) required the use of ethyl acetate besides ether for complete extraction of both



the salicyl acids and claimed to be able to separate salicyluric from salicylic acid in his quantitative method for the estimation of salicyl in urine, but Mosso also did not identify the supposed product as salicyluric acid. He concluded that most (up to 80 per cent) of the excreted salicyl in urine of man consisted of salicyluric acid, while in the dog the opposite was true. On the other hand, Baas (84) claimed that salicyluric acid can be completely extracted from acidified salicyl urine by ordinary ether alone. Using the method of Mosso, no salicyluric acid could be detected by Wiley (168) in the urines of human subjects taking salicylate. Nencki (146) claimed to have recovered salicyluric acid from urine by ether extraction of the acidified extractive obtained from urine treated with neutral lead acetate and then with alcohol. The melting point of his product was  $159^{\circ}\text{C}$  and the elementary analysis for carbon, hydrogen and nitrogen corresponded to the theoretical, but it is not clear how the figure for nitrogen was obtained. Nencki stated that the decomposition of salicyluric acid into glycocholic acid occurs easily in urine. Using a method similar to that of Nencki, and after the administration of salol and *b*-naphthol salicylic acid, Lesnik (45) obtained a product which melted at  $160^{\circ}\text{C}$ , and, from the analysis of the carbon and hydrogen content, he calculated the nitrogen content (without actual determination), and these figures put together corresponded to the theoretical formula for salicyluric acid. However, Lesnik doubted if salicyluric acid was the only salicyl product in urine. In his earlier work, Baldoni (178) asserted that he could demonstrate salicyluric acid in the human, but not in dog urine. In dog urine, two other salicyl compounds were obtained, one containing nitrogen, i.e., uraminsalicylic acid ( $\text{C}_{15}\text{H}_{16}\text{NO}_8$ ), and the other free of nitrogen, i.e., ursalicylic acid ( $\text{C}_{15}\text{H}_{14}\text{O}_8$ ). In uraminsalicylic acid, Baldoni claimed that the nitrogen was not in the amino form, but he failed to mention his tests. Both of these salicyl compounds gave an azure color with ferric chloride which Baldoni employed as the chief differential point from salicylic acid which gave a violaceous color. Similar modifications of the iron salicyl color reaction may occur in the presence of impurities and probably have no significance. Most of the salicyl in dog's urine, however, appeared uncombined, and only a small fraction as the two compounds. In later work, Baldoni (179) withdrew his former claims about the isola-

tion of salicyl glycuronic acid from human urine, and he regarded Neuberg's new product to be the same as his ursalicylic acid. He attached no importance to the use of lead acetate in the isolation of salicyl compounds from urine. In still later work on human urine, Baldoni (169) claimed that the data on the excretion of salicyl and salicyluric acids reported by Mosso and others were discordant, and, with his own method, claimed that the proportion of excreted acids after the administration of 5 grams sodium salicylate was 2.12 of salicyluric to 1 of salicylic acid. However, there was no identification of the salicyluric acid and the separation of the two acids was assumed to be complete by means of solvents. Nevertheless, Baldoni concluded that the greater part of administered salicyl is eliminated as salicyluric acid and that individual variations exist, but whether the conjugation can be facilitated or interfered with remained unsolved. From all that has been said, the unsatisfactory nature of the earlier reports on salicyluric acid is quite obvious. The more recent investigations, now to be discussed, are more critical, but no more decisive as to the regular occurrence of salicyluric acid.

It is obvious that before a product may be accepted as salicyluric acid it must possess certain physical and chemical properties that are distinctive and different from salicylic acid with which it is closely associated. Essentially this resolves itself into a determination of the melting point, estimation of the nitrogen content, and, if nitrogen is present, it must be shown that it exists in the form of an amino acid nitrogen. In addition, it is desirable to know the solubility in different solvents, since it is upon this that the separation of salicylic and salicyluric acids was based by many investigators. It is very essential that the products be pure, for, so far as nitrogen is concerned, this might be derived from the amino nitrogen of hippuric acid occurring normally in urine, or from other nitrogenous constituents. The lack of information on this point and the nitrogen content of the alleged salicyluric products in previous investigations is notorious. Depending on these criteria, Hanzlik (180) attempted to isolate salicyluric acid in the urines of 12 human subjects and of 8 dogs and 2 cats, receiving small, medium and full therapeutic doses of sodium salicylate. The methods of determining the melting point, solubility and nitrogen, of purification, etc., can not be considered in detail here but they were

of the usual standard kind. The test for  $\alpha$ -amino nitrogen was applied for the first time to salicyl urines in this study. This was done colorimetrically with the triketone hydrate (ninhydrin) reagent of Abderhalden which demonstrates conclusively the presence of the amino group in the alpha position, and, therefore, should be positive, as it was, with synthetic salicyluric acid and with hippuric acid. Pure synthetic salicyluric acid was prepared by the method of Bondi (181) and this and hippuric acid were employed as controls. Synthetic salicyluric acid may also be prepared according to the method of E Fischer (182). In addition, the methods of Bertagnini, U Mosso, Baldoni, Stockman and Nenckı and various modifications of these, and also other methods, were applied to the urines under various conditions, i e, freshly voided, preserved, standing and decomposed, with and without the use of heat. Briefly, the urinary extractives were completely negative for salicyluric acid, since all the criteria defined above were not fulfilled. The products that were obtained were not well characterized, did not have distinctive properties and glycocoll was not demonstrable. Therefore, it was concluded that salicylates were probably not converted into salicyluric acid in the living organism, and that the products that had been previously interpreted as salicyluric acid were presumably more or less impure salicylic acid. However, the more recent attempts of Drzimal (183) and of Holmes (167) indicate that some variable amounts of salicyluric acid may be removed from human urines.

Drzimal (183) reports the isolation of 0.98 gram crude salicyluric acid equivalent to about 13 per cent of the total salicyl residue of 7.3 grams from the urine of one patient receiving 5 grams of sodium salicylate. In other words, about 87 per cent of the salicylate excreted was excreted as such. Moreover, the total salicyl recovered by Drzimal from the urine with the hydrolysis-distillation method of Thoburn and Hanzlık (166) was 6.2 grams, which agreed quite well with the total of 7.3 grams of impure extractive recovered gravimetrically and from which the small quantity of 0.98 gram of salicyluric acid was obtained. This shows that the hydrolysis-distillation method is capable of recovering all of the salicyl products, including salicyluric acid, contrary to the claims of Holmes (167). Drzimal's salicyluric product was identified qualitatively by the same criteria as employed by

Hanzlik. Unknown quantities of the same product in some urinary extractives, and identified by essentially the same criteria, are reported by Holmes (167). By a procedure that is indeed questionable for the quantitative estimation of any nitrogenous product, let alone salicyluric acid, Holmes (167) arrives at the conclusion that for doses of sodium salicylate from 2 to 5 grams, the ratio of salicyluric to salicylic acid in urine is a constant at the value of 60 to 40 (1.5:1). This is quite different from the ratio claimed by Baldoni (169), namely, 2:12:1. However, the variability of these ratios is not surprising, since these investigators did not isolate, and conclusively prove they were dealing with, salicyluric acid in their quantitative experiments. Using Baldoni's method, Chistoni (171) claims that 79.89 and 73.37 per cent of the total urinary salicyl in two human subjects receiving 1 gram doses of acetylsalicylic acid were excreted as salicyluric acid. However, Chistoni did not isolate the product. Thus it appears from the most recent work that some salicyluric acid may appear in some urines after the administration of sodium salicylate, but that the occurrence in different species and its regularity and quantity are unsettled. It is not clear why some investigators have considered a conjugation of the compound with glycocholic an indispensable event, for salicylic acid, being a phenol as well as an acid, could conceivably conjugate with sulphuric acid with the excretion of ethereal sulphates. In fact, certain investigators have reported the excretion of ethereal sulphates, and of other salicyl products.

*Behavior of salicyluric acid in the body.* This can be studied with the synthetic product, which seems to be practically inert. Stockman (176) found that hypodermic injections in rabbits gave no symptoms, and it produced no beneficial effects in rheumatic fever. Stockman suggested that the administration of frequent and large doses of sodium salicylate in rheumatic fever is necessary because of its rapid excretion and rapid conversion into the inert salicyluric acid. Baldoni (184) reports that the acid is excreted unchanged and that hepatic lesions prevent its synthesis while kidney lesions probably favor it. However, the originals of his publications were not available. After 1.5 and 2 gram doses of salicyluric acid, Holmes (167) recovered 84 and 85.7 per cent in urine.

*Other salicyl products in urine.* It was mentioned in the beginning

and in other parts of this section that C Neuberg (144) reported the presence of salicyl ethereal sulphate, salicylglucuronic acid and oxysalicylic acids, that Baas (84) found the methyl and ethyl salicylates combined with ethereal sulphates and that Baldoni (178) found the uraminsalicylic acid and ursalicylic acids Holmes (167) denies the possibility of glucuronic acid existing in salicyl urines, and Ciamician and Ravenna (185) claim salicyl undergoes partial oxidation in the organism into compounds which are not easily extractable A product that has been extracted from dog's urine by Angelico (186) is gensitinic acid ( $C_7H_6O_4$ ) after the administration of sodium salicylate It was recovered with ether after acidification of the syrupy residue with sulphuric acid, is crystalline with a melting point of  $197^\circ$  to  $198^\circ C$ , and at  $210^\circ C$  decomposes into hydroquinone Chemically it is claimed to be oxysalicylic acid-2,5 Angelico concludes that in dogs at least salicyluric acid is not formed

*Excretion of salicyl in sputum* Excretion of salicyl and antipyrine in the sputum of diseased lungs, but not of guaiacol and terpenes, is reported by F Falk (187)

*Excretion of cinchophen.* Nothing definite is known about this Dohrn (188) believed cinchophen gave rise to hydroxy cinchophen and a number of other pyridine derivatives Skorczewski and Sohn (189) concentrated 30 liters of urine from a man receiving cinchophen, and after extraction of the concentrate with ether, obtained a product with a melting point of  $200^\circ C$  which they claimed was 2-phenylquinoline-4-carboxylic acid, an oxidation product of cinchophen Using the diazo reaction with urine after taking cinchophen, Greinert (190) found no change in the excretion of oxidation products and of residual nitrogen, but there was an increase in organic, inorganic and neutral sulphur Recently, Scheunemann (191) has made a study of the urine of rabbits receiving cinchophen and reported the presence of five products; a red pigment of unknown constitution, 5,6-dioxyquinoline, 8-oxyquinoline, 6-oxyquinoline and 6-oxy-4-quinoline (?) His method consisted of extracting with ether the concentrated urine previously acidified with hydrochloric acid, washing the ether extract with alkali and then applying certain tests to the brown, thick residue left after removal of the ether by distillation The residue was soluble in benzene, crystallized from amyl alcohol, gave a blue green color

with iron, and a red to reddish brown with Millon's reagent. These tests, it is claimed, excluded phenol and indicated dioxyquinoline, the *p* oxyquinoline giving with ferric chloride a weak yellow color. Scheunemann quotes Donath to the effect that the latter claimed oxidation of cinchophen to a pyridine-carbonic acid in the organism.

The expulsion of neocinchophen with the feces has been studied by Barbour and Lozinsky (86) and was discussed in the section on absorption. As only about one-third of the dosage administered (1.5 and 9 grams) was claimed to be absorbed, the urinary excretion of any products must be small.

### *Effects on metabolism*

**Nitrogenous** This is generally increased. Lessened urea excretion was noted in diabetic individuals by Furbinger in 1875 (53). Bohr (192) noted a marked increase in protein decomposition in dogs. Wolfsohn (193) observed in two animals a diminution followed by an increase in nitrogen excretion, in four animals there was from the start an increased urea excretion. The total nitrogen and uric acid in urine of patients taking 3 grams of sodium salicylate were found to be increased by Byasson (194). Chrone and Petrucci (195) observed in dogs and cats that prolonged administration of salicylate leads to emaciation and loss of body weight. The results of C. Virchow (196) confirm those of Bohr. Salomé (197) found that urea excretion was increased only after large doses of the salicylate. In Kumagawa's (78) experiments the increase in protein decomposition averaged from 10.6 to 13.4 per cent over the normal. This was compensated for by a loss during the after-periods. There was an increase in reducing substances in urine (about 60 per cent). The same was observed with salol. John (198) reports no influence on metabolism by salicylates. No definite conclusions can be drawn from the work of Tauszk and Vas (199) because of the uncertainty of the diet and the unreliability of the quantitative methods used. Goodbody (200) studied the distribution of nitrogen in urine during periods of salicylate medication. As compared with the normal, the specific gravity of the urine was increased, and this was due to increased excretion of nitrogenous substances, particularly urea. Ammonia was also increased. There was no effect on protein absorption. In Wiley's (168) subjects there

was a slight inhibitory effect on nitrogen metabolism. Creatinine nitrogen was slightly increased, urea unaffected, and ammonia decreased. There was an increased quantity of metabolized nitrogen or tendency to increased digestibility and absorption of nitrogen ingested. The specific gravity of the urine during salicyl periods was increased, the quantity of solids was also increased, and persisted through the after-period. This suggested that the katabolic activities of the organs were increased. The conclusions, however, are not fully convincing.

Under controlled conditions of dietary, etc., and using modern analytical methods, Denis and Means (201) demonstrated considerable increases (up to about 40 per cent) in the excretion of total nitrogen in two normal subjects and one septic individual receiving up to 6.6 grams of sodium salicylate. There were also increases in phosphates and uric acid during the salicyl periods, but the increase in total nitrogen tended to persist after the administration of salicyl. Recently, Ohtani (202) observed that moderate amounts not only of salicylic acid, but also of the *m*- and *p*-hydroxybenzoic acids, increase the nitrogen excretion in rabbits. On the other hand, large amounts, particularly of salicyl, diminish the excretion. This may be due to diminished excretory activity of the kidneys, which are injured by large doses, causing nephritis. Ohtani states further that all of the compounds increase the reducible constituents in urine, and that the *m*- and *p*-hydroxybenzoic acids always increase the ethereal sulphates of urine, but not salicylic acid.

*Uric acid* Owing to the fancied connection of uric acid with the etiology of acute articular rheumatism, the earlier literature contains several contributions on the effects of salicylates on the excretion of this purine. These are now chiefly of historical interest, but are remarkable for the uniformity of agreement on this phenomenon, which has been confirmed by the latest researches. As early as 1877, G. Sée (150) thought that salicylate increased the excretion of uric acid in gout. Blanchier (97) thought that salicylate increased uric acid excretion in normal as well as rheumatic individuals, urea excretion was also increased. Marrot (203) found uric acid excretion to be increased in individuals suffering with rheumatic fever, lessened in fever-free subjects. In observations on himself, Salomé (197) found

that only large doses of salicylate increased the uric acid excretion. In dogs, Kumagawa (78) found the excretion to be increased from 31 to 45.6 per cent. Schreiber and Waldvogel (204) reported a constant increase in uric acid excretion. The most marked increase in uric acid excretion occurred on the third day of salicylate medication in a subject studied by Herter and Smith (205). Siegert (206) found excretion to be lessened. Herringham and Davies (207) observed an increase in excretion, but were not satisfied that the presence of salicyl in urine did not interfere with uric acid determination. In diseased conditions, a decreased uric acid excretion was noted by Martineu (208) in typhoid fever, of uric acid, urea and phosphates by Bouchard (cit. Blanchier (97)). Unfortunately, many of these earlier observers took no account of the dietary régimes, though the estimations were frequently made in 24-hour collections of urinary specimens.

Later work, carried out by modern and more reliable methods, supported the views of the older investigators, namely, that salicylates increase the excretion of uric acid. The increased excretion observed by Bohland (209) was considered to be the result of increased uric acid production, and was ascribed to the concomitant leukocytosis. Hack (210) also observed an increased uric acid excretion after salicylate, and also ascribed this to leukocytosis, but, as no statement is made when the leukocyte counts were made, it is difficult to judge of any existing relation between the increase in uric acid and the leukocytosis. With subjects on a constant protein diet, sodium salicylate was found by Schreiber and Zaudy (211) and by Schreiber and Waldvogel (204) to cause a greater excretion of uric acid than salicylamide, and these increases bore no relation to leukocytosis, which was variable and often lower at the time of the greatest increase in uric acid excretion. Lewandowski (212) reported that benzoic and quinic acids, as well as salicylic acid, increased the excretion, but gave no metabolic controls. In dogs, which were kept on a constant diet and fluid intake, Singer (213) found that acetylsalicylic acid increased uric acid elimination and suggested that this was due to a simultaneous increase in leukocytes.

In experiments on himself in nitrogen and phosphate balance, Unger (214) confirmed the work of previous observers, and found



that uric acid excretion was increased by sodium salicylate from 40 to 50 per cent Ulrici could draw no conclusions as to the effects on leukocytes, since the counts were too dissimilar and since increases occurred also when no salicylate was taken According to Hall (215), the endogenous purines in urine are increased by the administration of sodium salicylate, and this increase does not arise from excessive cell destruction, but probably from diminished destruction of the uric acid already present Wiley (168) concluded from observations on 12 subjects that uric acid was decreased, but the figures indicate practically no change in the excretion; yet there was an increase in leukocytes in the blood Rockwood (216) found acetylsalicylic acid to increase the excretion of uric acid, and concluded this to be due to an inhibition of the uricolytic ferment rather than to destruction of nuclein, since there was no simultaneous increase in excretion of phosphoric acid Approximately a 30 per cent increase in uric acid excretion lasting till the end of the second day was reported by Dreser (11) after 2.2 grams acetylsalicylic acid administered to a subject on a constant diet

The following interesting features regarding the effects of salicylates on uric acid excretion have also been described Stookey and Morriss (217) found that the liver, kidney, spleen and muscles of dogs given sodium salicylate (0.1 gram per kilo) increased the decomposition of uric acid as compared with the organs of untreated animals The time of exposure was from 44 to 144 hours, the treatment of the dogs lasted from 5 to 10 days, and 9 to 65 grams of the organs were used Waucomont (218) reported that sodium salicylate diminished the excretion of uric acid and xanthine compounds in chickens with experimental gout produced by feeding horse flesh over long periods of time According to Pohl (219) allantoin excretion is not increased by salicyl, but Nagashima (220) claims that it is, and that this holds for cinchophen and the benzoic and quinic acids as well as for salicyl Before going to the mechanism of the increase in uric acid excretion, the reports on cinchophen will be presented

An increase in uric acid output after administration of cinchophen was originally observed by Nicolaier and Dohrn (28), and confirmed by nearly all later investigators among whom were Weintraud (221), Plehn (222), Retzlaff (223), Schittenhelm and Ullmann (224), Wie-

chowski and Bass (225), Zuelzer (226), Skórczewski and Sohn (227), and Kehrér (228). However, the explanations of the phenomenon were varied and none was satisfactory. Nicolaier and Dohrn thought the increase was due to a "toxic" production of uric acid, Skórczewski and Sohn to a diminished oxidation, and Kehrér to stimulation of the enzymatic conversion of purine bases to uric acid. Brugsch (229) claimed that cinchophen mobilized deposited urates and this idea is being exploited even today despite the untenability of the notion on the basis of well known physical and chemical properties of the urates. Starkenstein and Wiechowski (230) claimed that cinchophen depressed the purine metabolism as indicated by the reduced excretion of allantoin in animals and by the reduced excretion of uric acid during the after-period in man. This metabolic action was claimed to be inconstant, and in gout the greater elimination of uric acid excretion was accounted for on the basis of a greater amount of the metabolite available from deposits. In later observations, Starkenstein (231) claimed that the cinchophen caused only a temporary increase in uric acid excretion by healthy subjects on a purine-free diet without further increases after administration of the drug during the subsequent period of diminished excretion. He argued that the increased excretion could not be due to increased formation, since in animals there was no demonstrable increase in allantoin output under similar conditions. Furthermore cinchophen retarded the action of purine-forming enzymes in the liver, especially the xanthine-oxidase. In contrast with cinchophen, calcium chloride decreased the excretion of both uric acid and allantoin and retarded the activity of purine-forming enzymes, and radium emanations increased the output of uric acid in man and of allantoin in rabbits. Weintraud (221) advanced the view that the drug exerted a selective action on the kidney and through this action removed uric acid from the body. Retzlaff (223) concurred in this view.

The older explanations of the increased uric acid elimination varied according to the views concerning the nature of purine metabolism and of gout and rheumatism. Urinary analyses alone could not settle the question and the older quantitative methods based on isolation of the metabolite were inadequate. The few blood analyses reported were unreliable. There was also some confusion from the fact that the

total nitrogen of the urine was not always increased during the uric acid increase. According to modern work on the subject, salicyl increases the total nitrogen excretion. Nevertheless, so far as the mechanism of the increased uric acid excretion is concerned, this seems to be the same for both salicyl and cinchophen and is concerned with the kidney rather than with some obscure change in metabolism or mobilization of the urates in the tissues. Pietrulla (232) observed that large (6 grams daily) doses of salicylic acid increased the excretion of uric acid from 0.25 to 0.6 gram in normal subjects on a purine-free diet, and suggested that the point of attack was similar to that of cinchophen. However, it remained for Folin and Lyman (233) and Denis (234) to demonstrate conclusively that the mechanism of the increased excretion by these drugs is identical.

*Mechanism of the increased uric acid excretion by cinchophen and salicyl.* Using the colorimetric method of Folin and Denis (235) for uric acid in urine and blood, Folin and Lyman (233) demonstrated that single and repeated doses of 3 and 5 grams of cinchophen invariably increased the uric acid in urine and simultaneously decreased its content in the blood of 5 convalescent subjects and one patient suffering with gout. These investigators concluded that the increased output represented the elimination of uric acid which had previously accumulated in the blood, and that the previous accumulation represented a corresponding kidney inefficiency. The cinchophen caused a diminution of the non-protein nitrogen and urea whenever these were present in the blood in usual amounts. This was in accord with the ideas of Weintraud (236), who demonstrated diminution of "rest" nitrogen of the blood after cinchophen. Folin and Lyman's gouty patient responded the same way as the convalescents, and, since the uric acid content of his blood increased on withdrawal of the drug, they concluded with Weintraud (221) that the action of the drug was on the kidney. Following Folin and Lyman, McLester (237) and Steinitz (238) also demonstrated that cinchophen lowered the uric acid content of the blood. Definite evidence of the similarity of the increased uric acid excretion after salicyl to that after cinchophen was supplied by Denis in 1915 (234), who showed, that after doses of 7 grams and over of sodium salicylate administered to 13 subjects on a purin-free dietary and suffering with different disease conditions, there

was a definite increase in uric acid excretion in urine with a simultaneous decrease in the uric acid content of the blood. From this it was concluded that salicylate lowered the threshold of the kidney for uric acid, and this increase in renal permeability was thought to hold not only for uric acid but also for other waste products including the supposed toxins of rheumatic fever. However, the non-protein nitrogen of the blood was not always increased during the increased output of uric acid, and doses of 3.3 grams of the salicylate in some cases gave negligible changes in the uric acid. Nevertheless the results on uric acid agreed with those of Folin and Lyman (233) on cinchophen, and, hence, the mechanism of action of the two drugs was thought to be identical.

However, Frank and Pietrulla (239) feel that the last word on the subject of uric acid excretion by cinchophen has not been said, and they criticize the colorimetric method used by Folin and Lyman (233). There is no doubt that the uric acid reagent of Folin and Denis (235), which is also a reagent for phenols, can not differentiate between uric acid and salicyl and probably also the products after cinchophen. The increased values for uric acid, therefore, are due in part to these drugs and their products in the urine. This has been indicated by unpublished experiments in this laboratory, but the study has not been carried sufficiently far enough to show how far the results on uric acid excretion may require modification. However, it seems quite obvious that the salicyl, and also cinchophen, of the urine should be removed before the colorimetric reagent is applied. On the other hand, the lower figures for uric acid of the blood reported by Folin and Lyman, Denis and others are not consistent with an expected increase from the salicyl of the blood during the medication. The subject merits further study with another method. Ample confirmation of the difference between the uric acid content of the blood and urine by the colorimetric method after both salicyl and cinchophen, however, has been reported by several investigators.

Confirmation was reported by Fine and Chace (240), who administered cinchophen to patients, while radium bromide given intravenously or by inhalation of the emanations, did not affect the uric acid content of the blood. Later on, Fine and Chace (241) showed that sodium salicylate in from 3- to 6 gram daily doses and a 2-gram

reduced the uric acid of the  
initial content, the urinary  
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After the administra-  
up to about 10 grams) of  
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It appeared also that  
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uric acid was retarded and the absorbed amounts could not be recovered quantitatively. Against uricolysis was the fact that more uric acid was excreted than was injected. It was suggested that uric acid formation occurred under the stimulus of the injection. According to Graham (251), the source of the increased uric acid of the urine can not be the blood, since the total amount is too small, and the evidence that uric acid deposited in the tissues can be redissolved is too weak. Using the colorimetric method of Folin and Denis with blood and the Folin-Shaffer method for urine, A. Wolff (252) reported recently that intravenous injections of sodium cinchophen, in doses of from 0.5 to 2 grams used as a 10 per cent solution, did not reduce the blood uric acid of 7 starved patients suffering with bronchitis, plumbism, arteriosclerosis, arthritis, chronic nephritis and hydronephrosis. The uric acid of the urine was increased. The absence of change in blood uric acid, he thinks, argues against the tissue mobilization theory, and whether the increase in urine is due to an action on the kidney or nervous system is unsolved. As far as the blood uric acid results of Wolff are concerned, the failure to demonstrate a decrease may be due to the use of the colorimetric reagent reacting with the cinchophen, or its products in the blood, thus giving false values for uric acid. Rosenfeld (253) conceives of cinchophen, glycerine and alcohol acting the same way on uric acid, that is, by oxidation of exogenous and endogenous purines, but this seems rather speculative. An increase in the output of nucleic acid in the urine of normal individuals continuing more than three days after the administration of cinchophen is reported by Grabfield and Pratt (254). The increase exceeded the endogenous level. These observers report that cinchophen does not invariably "sweep out" the uric acid from the body of normal individuals. The oxidation product appearing in urine after administration of cinchophen to man, namely, hydroxyphenylquinoline carboxylic acid, is reported by Rotter (255) to increase the elimination of uric acid just like cinchophen itself. According to Borak (256), marked excretion of uric acid takes place also after irradiation of the liver and spleen by x-rays, and comparing this with the increases after administering cinchophen and drinking large quantities of water, he concludes that the mechanism of the excretion of these agents is similar, namely, a washing out of purines from the tissues. However, this does not follow from the mere similarity of effects.

Recently, Goldwasser (257) has observed that the amount of uric acid changes in surface tension in a 24-hour urine were more or less parallel after administration of cinchophen. The factor  $E = (a - b) Q/100$  (in which  $Q$  represented the volume of urine,  $a$ , drops of urine and  $b$ , drops of water, by stalagmometer) and the amount of uric acid increased simultaneously on the addition of meat to a purine-free diet, but after the administration of cinchophen,  $E$  decreased although the uric acid increased. Recently, Stern (258) studied the comparative solubility of uric acid in salicylate and cinchophen. The solubility in 1 per cent sodium salicylate was double that in water, and trebled in sodium cinchophen. The increased solubility in salicylate was not due to the formation of sodium urate, since salicylic acid is a stronger acid than uric acid, and, therefore, it was suggested that the increase was due to some hydrotropic effect. In the case of cinchophen, the cause of the increased solubility was unknown, since the dissociation constant of cinchophen is unknown. Confirmation under controlled conditions (pH, etc.) is desirable before the results can be of significance in the prevention of uric acid deposits in urine. As for urate deposits in tissues, such experiments should at least be made with sodium acid urate in serum under the proper conditions of pH, carbon dioxide tension and temperature to be of physiological significance.

*Sulphur* An increased excretion of sulphur in the urine, chiefly as sulphate ( $\text{SO}_4$ ), was observed by Baumann and Herter (259). An increase amounting to from 10 to 19.6 per cent above normal was reported by Kumagawa (78). This was compensated for by a loss during the after-periods. The normal constant relationship between total nitrogen and sulphur became irregular during salicyl medication. Ethereal sulphates were found to be uninfluenced by Baumann and Herter (259), Moreigne (260) and Singer (213). Moreigne found the total sulphur, urochrome and phosphates increased. Wiley (168) found the relative percentages of ethereal and inorganic sulphates to be unaffected, only the relative proportions of neutral sulphur appeared to be increased. Combinations of salicyl with ethereal sulphates were mentioned in the fore-part of this section in conjunction with other salicyl products in urine.

*Glycosuria and glycuronic acid* In connection with the discussion

of general excretion, it was indicated that at least three of the older reporters claimed reduction of Fehling's solution by salicyl urines. More recently, Kramer (261) reports that Trommer's test was positive with urines of a large number of individuals receiving acetylsalicylic acid. However, reduction of Fehling's solution is denied by Holmes (167), who contends that the absence of the sugar reaction is proof against the occurrence of glycuronic acid. No salicyl glycuronic compound was found with color tests. The fermentation test might not be satisfactory in the solution of the question owing to the possibility of some antiseptic action of salicyl urines, especially the highly concentrated ones after full therapeutic doses of the drug.

*Reaction of urine* The acidity of urine is increased during salicylate medication according to Moreigne (260), Schreuder (262) and Jordan (56). No effect on the reaction was observed by Wiley (168).

*Respiratory metabolism* Singer (213) claimed an increase in the oxygen consumption of rabbits after toxic doses of acetylsalicylic acid. However, Denis and Means (201) observed no changes in the respiratory quotient of 2 normal individuals and 1 septic patient receiving doses of sodium salicylate up to 6.6 grams. The spirometer type of apparatus was used under controlled conditions of dietary, etc.

### *Autolysis*

This was observed by Lacquer (263) to be increased in muscles with weaker solutions of sodium salicylate (0.1 per cent), inhibited by stronger solutions (1 per cent). Dogs poisoned with large doses of sodium salicylate exhibited no increase in soluble nitrogen in fresh organs (liver and muscle), and there was no special rapid autolysis of these organs.

### *Blood*

*Reaction and acidosis* The symptoms of salicylism have been attributed by some to acidosis. Also the administration of bicarbonate, which is commonly given with salicylate, has been justified on this basis, i.e., to prevent the occurrence of acidosis. However, it is hardly conceivable that the true reaction (hydrogen ion concentration) of the blood could be sufficiently altered by salicylate so as to cause real acidity, and the results of old and recent observations con-



firm this opinion As early as 1883, H H Meyer (264) showed that sodium salicylate could inhibit oxidation but it did not influence the alkalinity of the blood Walter (265) claimed that death in fatal poisoning from salicylates does not result from the production of acidity, since the blood of animals so poisoned contained insufficient (only 11.2 per cent by volume) carbon dioxide

Using the colorimetric-dialysis method of Levy, Rowntree and Marriott (266) for pH, and the colorimetric-dialysis-aeration method of Marriott (267) for alkali reserve, of the venous blood of seven rheumatic and non-rheumatic individuals receiving full therapeutic doses of sodium salicylate to the point of salicylism, Scott, Thoburn and Hanzlik (122) found no noteworthy changes in the reaction and reserve alkalinity of the blood at "toxicity" The same was found to be true of 2 dogs and 2 cats treated with corresponding and larger doses of the salicylate Moreover, the administration of approximately equal doses of bicarbonate and salicylate to 6 convalescents by Hanzlik, Scott and Thoburn (162) and Hanzlik, Scott and Reycraft (163) did not alter the "toxic" dose or prevent the symptoms of salicylism This disproves the claim of Lees (268) that the administration of bicarbonate with salicylate modifies and prevents the symptoms of salicylism, and even convulsions It is also against the claim of Delore (269) that bicarbonate prevents the side actions of salicylate As far as systemic effects are concerned, Meara (270) is probably correct in his belief that the use of alkalies together with salicylates has been dictated more by tradition than by any rationale

*Salicyl and enol acids* It is interesting to note, however, that salicyl causes considerable acceleration of respiration with symptoms of air hunger just like certain enol acids occurring in diabetic acidosis A state of ketosis appears to have occurred in each of 3 cases of poisoning from methyl salicylate reported by Rosenbloom (271), H B Myers (272) and Wetzel and Nourse (273) In all these cases there was some resemblance to diabetic coma and all 3 urines contained acetone, and 1 urine, diacetic acid Moreover, Hurtley and Trevan (274) have reported that the subcutaneous and intravenous injections of sodium salicylate, ethyl acetoacetate, sodium acetoacetate and acetyl acetone in animals caused the phenomena of diabetic coma None of these compounds caused changes in the pH of the blood, but all caused air

hunger and coma with increased pulse rate and final respiratory failure. The results agreed with the hypothesis that the phenomena of diabetic coma are due to poisoning by aceto-acetic acid in the form of salts and not to true acidosis. The enolic group,  $-C(OH)=CH-$ , which occurs in one form of ethyl acetoacetate and gives a color reaction with iron, is claimed to be 18 times as active as *B*-oxybutyric acid. Bearing in mind that salicyl also gives a color reaction with iron and markedly accelerates respiration, there may be possibilities in this interesting physiological conception in explaining certain features not only of the actions of salicyl but also of respiration itself.

*Erythrocytes* The direct application of salicylic acid to red blood corpuscles tends to cause disintegration. Cotton (275) observed that a 3 per cent solution caused them to become globular and the hemoglobin was decomposed with the formation of hematin. Thiersch (276) noted that the central portion of the corpuscles became transparent and enclosed by a peripheral zone of yellow that broke up into segments which floated in the plasma. Swelling and discoloration of frog erythrocytes was observed by Prudden (277) with solutions of 1:1000 salicylic acid, and decolorization with destruction by solutions of 1:500. Human erythrocytes swelled and decolorized with concentrations of from 1:4000 to 1:1000, and became markedly degenerated with 1:500. After internal administration of salicylates, Marrot (203) saw a diminution in number of red blood-corpuscles. On the other hand, a slight increase in the number of both white and red corpuscles was observed in the metabolism experiments of Wiley (168).

*Leukocytes* With dilute solutions of salicylic acid, Binz (278) observed a paralytic action on white blood-corpuscles, similar to that produced by quinine, and death with concentrated solutions. Cotton (275) found that a 1 per cent solution of salicylic acid caused the central portion of leukocytes to become transparent, and gave them a double contour. Prideaux (54) observed the movements of leukocytes to be depressed by salicylic acid, but the red corpuscles remained unaffected. Prudden (277) obtained results as follows with the leukocytes of frogs, rabbits and man. With frogs, 1:4000 of salicylic acid in 0.5 per cent sodium chloride solution checked the emigration of leukocytes in the bladder and mesentery without alteration of the caliber of the vessels, the structure of the cells remained unaffected, but

Salicyl salicylate is practically tasteless, and methyl salicylate has the burning, disagreeable taste of volatile oils. The liberation of free salicylic acid from the esters in the alimentary tract has been discussed in the section on absorption, and other aspects of local action have been pointed out in the section on local action and irritation.

Cinchophen, being an acid, also causes local irritation and considerable gastric distress, but not so neocinchophen, which is an ester and less soluble. Gastric irritation and anorexia from cinchophen were observed by Heller (290) and this was fully confirmed by Hanzlik, Scott, Weidenthal and Fetterman (291) in a study of 17 human subjects receiving variable doses of the drug. These symptoms were generally absent after large doses of cinchophen in 10 other subjects. Absence of gastric distress after doses up to 16 grams of neocinchophen was reported by Barbour, Lozinsky and Clements (292), a similar claim being made also by Chace, Myers and Killian (293). However, Miller and Boots (294) observed quite as much abdominal distress after neocinchophen as after salicylates. In a later study, Miller and Boots (295) reported that these symptoms were milder in degree after the administration of the ethyl ester of cinchophen, which differs chemically from neocinchophen by the absence of the methyl group.

*Emetic action* This occurs with all the salicyl and cinchophen compounds providing sufficient dosage is administered. The cause is unquestionably central with salicyl, and presumably also with cinchophen. In 1879, Blanchier (97) observed that sodium salicylate caused vomiting whether given gastrically or intravenously. In his study of the toxic and fatal doses of different salicyl compounds, Waddell (296) found animals to vomit quite as readily after intravenous as after oral administrations, and the salicyl was not found in the vomitus after hypodermic administration. But it remained for Eggleston and Hatcher (297) to demonstrate conclusively that the seat of the emetic action is central. This was done on three eviscerated dogs which responded to doses of 0.2 and 0.3 gram of sodium salicylate intravenously with nausea in  $1\frac{1}{2}$  minutes and with vomiting movements in from  $4\frac{1}{2}$  to 10 minutes after injection. Oral administration resulted in delayed vomiting and the dosage required was three times that intravenously, or, in other words, emesis did not occur from the local action, but only after adequate absorption and systemic action of the drug.

That the various derivatives (esters, etc) of salicyl and cinchophen cause nausea and emesis in human subjects is readily seen from the reports of the following investigators Hanzlik (298), Hanzlik, Scott and Thoburn (162) and Hanzlik, Scott and Reycraft (163) on sodium salicylate, Hanzlik and Prescho (21, 23, 24) on acetylsalicylic acid, salicyl salicylate and methyl salicylate, Hanzlik, Scott, Weidenthal and Fetterman (291), Miller and Boots (294, 295), Chace, Myers and Kilian (293), and Heller (290) on cinchophen, neocinchophen and the ethyl ester of cinchophen Barbour and Loziusky (299) did not observe emesis with the highest doses of neocinchophen in dogs, while doses of 0.5 gram of cinchophen and of 0.1 and 0.2 gram of acetylsalicylic acid caused emesis. Nausea and vomiting are also among the symptoms of poisoning reported by several to be discussed later in the section on toxicity. From the fact that the salicyl derivatives circulate through the tissues unchanged to a considerable extent (discussed in the section on excretion), it is indicated that they were mainly responsible for the nausea and emesis which occurred in the same subjects. As far as salicyl salicylate ("salysal," "diposal") is concerned, this is contrary to the claim of Minkowski (300), and liberation of salicylic acid does not occur in the stomach as claimed by Tocco-Tocco (301) and proved by the work of Hanzlik and Prescho (23).

**Secretions** The secretions of the accessory glands of the alimentary canal are increased at first, later diminished, according to Blancher (97), who investigated this in dogs. In 4 to 5 minutes after intravenous injection of about 0.3 gram per kilo of the sodium salicylate, the increase in saliva became noticeable, which gradually increased up to 5 times above normal and continued for some time. After increasing the dosage, the secretion stopped almost entirely. The same sequence of phenomena was noted with bile. Pancreatic juice remained practically unaffected. Blancher regarded the hypersecretion of saliva as due to a central action on secretory nerves, and the inhibiting action as due to a local action on the glandular elements in part, and partly to a paralyzing action on the nervous system. Hypersecretion of bile and saliva were also noted after gastric administration, although occurring somewhat later. In Wiley's subjects (168) there was a diminution of the total quantity and the water content of the feces. There was no tendency to produce diarrhea. The

dosage ranged from 0.2 to 2 grams per day, and about 30 grams were administered in thirty days. A marked increase in gastric secretion has been observed by Leichentritt (302) after administration of sodium salicylate, acetylsalicylic acid and salol to dogs with duodenal fistulae and on a diet of flesh and milk. The control secretion was from 296 to 365 cc, after acetylsalicylic acid, 420 to 457 cc. The action resembled that of arsenic compounds.

*Cholagogue action* The reports on this are contradictory, diametrically opposite results being reported with the same experimental methods. This is not surprising, since the operative procedures commonly employed in experiments for the purpose are apt to disturb the functions of the liver and the biliary passages, and this seems to be true of both acute and chronic experiments. The older investigators generally recorded increases in the secretion of bile after salicyl. Blanchier (97), Stadelmann (303) and Mandelstamm (304) found increases in dogs after sodium salicylate, and Pfaff and Balch (305), after salol. Urobilin in urine after salicylate was reported by Dominikiewicz (306). Petrowa (307) demonstrated, in dogs with gall-bladder and gastric fistulae and ligated ductus choledochus, that sodium salicylate increased the secretion of bile, and this was generally true of those compounds that are conjugated with ethereal sulphates. On the other hand, Smyth and Whipple (308) claim no effect from sodium salicylate, in therapeutic doses, on the excretion of bile salts in dogs with permanent biliary fistulae. Negative results also have been reported recently by Stransky (309) after doses of 0.1 and 0.2 gram sodium salicylate intravenously and intraduodenally in rabbits. These were acute experiments in which the cystic duct was ligated, and the bile and its solids measured after collection from a cannula in the ductus choledochus. Stransky states that his negative results agreed with those of Pohl and of Brugsch and Horsters on dogs with fistulae. In guinea pigs receiving methyl salicylate orally and hypodermically, Leone (310) observed a marked increase in the total amount of bile secreted, but the percentage of dry matter and ash was decreased. The viscosity and surface tension of the bile were diminished, while the osmotic pressure and electrical conductivity were increased, all of these changes being directly proportional to the amount of the ester administered. With the larger doses by mouth, the ester was

excreted into the bile. In another series of experiments with guinea pigs on a constant diet, Leone (311) confirmed that hypodermic injection of methyl salicylate increased the amount of bile secreted, but the total solid residue was also increased. Apparently the increase in secretion was out of proportion after doses of 1 gram as compared with doses of 0.25 gram.

The results with cinchophen are no more satisfactory than those with salicyl. In their studies with gall bladder fistulae, Brugsch and Horsters (312) found that intravenous, intramuscular and oral administrations of sodium cinchophen in doses of from 0.8 to 3 grams caused increases in secretion of bile from 8 to 864 per cent. The total quantity, solids, acids and pigment of 24-hour collections of bile were all increased, likewise the viscosity and surface tension quotients. The viscosity quotient for normal bile was between 2.4 and 11, and administration of cinchophen changed this to 16, 20 and 39. The alkalinity of some biles was increased, that is, the pH determined electrometrically increased from 7.4 to 7.98 before, to 8.3 after, cinchophen. A considerable increase in secretion of bile was produced in atropinized dogs, and therefore the augmentor action of cinchophen was not concerned with the autonomic nervous system. It was thought to be due to direct stimulation of the liver cell. Since quinine, optochin and carbohydrates also possessed a cholagogue action, there was nothing peculiar to or specific about cinchophen. Further confirmation of the action of cinchophen is reported by Horsters (313), who attributes it to an effect on the liver cells and attempts to reconcile it with the increase in uric acid excretion produced by the drug. However, Stransky (308) reports he was unable to confirm the work of Brugsch and Horsters. Using doses of from 0.05 to 0.2 gram of sodium cinchophen in 5 per cent concentration intravenously and intraduodenally in urethanized and unanesthetized rabbits, the secretion of bile was unchanged or diminished. Ether extraction of the acidified bile failed to reveal the presence of cinchophen in the secretion.

Clinically, intravenous and intramuscular injections of cinchophen in healthy subjects and patients with catarrhal jaundice are reported by Grunenberg and Ullmann (313) to have caused increases in the bile (ash and pigment) of duodenal contents and in the bilirubin content of serum. Unfortunately, the dosage is not stated, and in some cases

proprietary products were used one of which was a mixture of salicylate and cinchophen. Using the same method, i e, the duodenal tube in patients, Teschenberg and Hoffmann (314) claim confirmation of the stimulating action of cinchophen on bile, magnesium sulphate, oil of peppermint and sodium glycocholate acted similarly Slobosiano and Herscovici (315) report that daily doses of 0.1 gram of cinchophen together with 2 grams of sugar by mouth reduced the bilirubin content of the blood of 6 jaundiced infants, but taken without sugar the drug was vomited and no change in the blood was observed. The drug was also not retained when given in 0.1 gram doses twice daily per rectum.

*Salicyl as a test of liver function* The use of salicyl for this purpose is uncritical, for the liver is not the sole organ in which transformation or destruction of salicyl may take place. In dogs with hepatic degeneration from phosphorus, Hanzlik and Wetzel (26) found the urinary excretion of salicyl to be quite as prompt and as good as in normal control dogs, and hashed liver caused no more destruction of salicyl than other organs. Therefore, these results did not support the statement of Dixon (317) that salicyl is chemically changed by the liver.

Moreover, the clinical reports on the use of salicyl as a test of liver function are distinctly uncritical. Roch (318) claims that the normal liver transforms 0.04 gram sodium salicylate taken one hour after breakfast, so that none can be found in urine during the next 5 hours, while, in hepatic insufficiency, a positive test with ferric chloride is obtained within this time. Roch claims further that salicyl induces formation of glycuronic acid in the liver, and that he has obtained reliable results in 100 patients. The claim as to glycuronic acid is unsupported by evidence, and as for the test of liver function, which depends on urinary excretion of salicyl, this is uncritical without quantitative estimation, and consideration of diuresis and factors influencing absorption, destruction, etc. Herissey, Fiessinger and Debray (319) claim that 0.2 gram sodium salicylate gives in normal subjects a urinary reaction with iron lasting about 6 hours, but, in cases of cirrhosis, the reaction is not so well marked. This is attributed by these authors to mechanical conditions resulting from portal stasis, etc., but, of course, under these conditions the intestinal absorp-

tion would be impaired and excretion diminished. Without estimations under controlled conditions, the test would have no meaning anyway.

*Cinchophen and salicyl on excised intestine* According to Starkenstein (320), direct application of sodium cinchophen to segments of rabbit intestine causes depression and paralysis. With excised loops of rabbit and guinea-pig intestine, used according to the Trendelenburg method, Starkenstein (321) found sodium cinchophen (0.4 cc, 10 per cent) and 'leukotropin' (0.3 cc, 40 per cent of a mixture con-

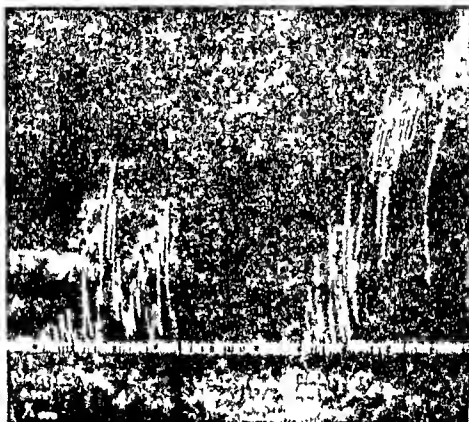


FIG. 3 SENSITIZATION OF RABBIT'S INTESTINAL MUSCLE TO PITOCARPINE (1:50,000) BY SALICYLIC ACID (1:25,000)

taining 0.5 gram cinchophen and 1.5 grams hexamethyleneimine in 5 cc.) to cause an immediate, fleeting and moderate stimulation followed by depression and paralysis of these organs. Using the same mixture containing cinchophen, Ullmann (283) claims the typical effect on excised segments of guinea pig intestine is parasympathetic stimulation characterized by increased tonus and peristalsis and antagonism by atropine. These results are supposed to have a relationship to the leukopenia after cinchophen which is assumed to be a "vagus shock."



In concentrations of from 1.800 to 1 160, sodium salicylate was found by Alvarez (322) to cause initial stimulation followed sometimes by depression of excised strips of different portions of rabbit intestine. There was also a tendency to reverse the gradient, which seemed to agree with the tendency of the drug to upset the stomach.

*Sensitization of excised intestine by salicylic acid* An interesting sensitization of rabbit intestine by salicylic acid to pilocarpine and barium has been demonstrated by Thienes (323). No effects resulted from the direct application of concentrations of from 1 50,000 to 1 25,000 of salicylic acid, but on the addition of salicylic acid either during or preceding the actions of pilocarpine and barium, the responses to the latter drugs were increased 50 per cent. Figure 3 illustrates a sensitization to pilocarpine. Sodium salicylate, in concentrations of from 1.30,000 to 1.10,000, caused no alterations in the drug responses. The increased response of the intestine to pilocarpine and barium caused by the salicylic acid was probably a cell surface effect in virtue of the lipid solubility of the salicylic acid, the sodium salicylate giving negative results because it is not lipid soluble. This sensitizing action is not peculiar to salicylic acid, but occurs with a variety of agents capable of changing the environment of cells and their surfaces, and therefore their functional state and response to stimuli. The result is of interest in connection with the fundamental aspects of allergic phenomena, but should not be transferred directly to explain the peculiar idiosyncrasies toward acetylsalicylic acid occurring in man.

### *Kidney*

The kidney is affected by both salicyl and cinchophen in therapeutic and toxic doses. This is indicated by the increased permeability to uric acid and possibly other metabolites discussed in the section on metabolism, by the changes in urine output, morphology and functional efficiency and by albuminuria.

*Diuresis* According to the reports of Blanchier and Bochefontaine (324), Carrieu (325), Blanchier (97), Marrot (203), Huber (326), Chopin (327), Siegert (206), Bardier and Frenkel (328), and Schreuder (262) diuresis is moderately increased in human subjects and animals receiving small and moderate doses of sodium salicylate. Huber's

results on human individuals agreed with those on rabbits with ureteral catheterization. During periods of increased diuresis after 0.03 to 0.06 gram per kilo in dogs, Bardier and Frenkel observed an increase in kidney volume due to vasodilation, and this was followed by vasoconstriction with diminution in flow of urine. Moreigne (260) reported a diminution in diuresis. Wiley (168) observed practically no change in the volume of urine during 24-hour periods after administration of 0.2 to 2 grams per day (average 1 gram) for 30 days. In the after-periods there was a decrease. Cornet (154) found salol to have no influence on diuresis.

On the other hand, full therapeutic doses of sodium salicylate diminish the diuresis in rheumatic and non-rheumatic individuals. This was definitely demonstrated in 13 non-rheumatic and convalescent and five rheumatic individuals by Scott and Hanzlik (329) and Hanzlik, Scott and Reycraft (163). All the subjects were on a constant water intake and the urine was collected in 10-hour periods. The total dosage of salicylate ranged from 9.4 to 22.4 grams administered in 1 gram doses hourly until symptoms of salicylism supervened. The diminution in urine output varied considerably. Some of the subjects showed a temporary increase in diuresis at the time of symptoms of salicylism, but the predominant effect in the majority was a diminution in diuresis. The latter was due in part to diaphoresis, and in part to diminution in renal functional efficiency. The sweating was especially pronounced in rheumatic individuals. The diminution in renal function was demonstrated in the non-rheumatic individuals whose body weight increased unless modified by diaphoresis. The greatest diminution in diuresis was demonstrable at the end of about 30 hours after administration of the salicylate and lasted till the end of about 60 to 70 hours, i.e., practically till the completion of the salicyl excretion. The diminution in renal functional efficiency was indicated by an increase in urea of the blood, a decrease in excretion of phenolsulphonephthalein, and by albuminuria occurring simultaneously with the decrease in urine output. A summary of the results on diuresis and related phenomena after administration of full therapeutic doses of sodium salicylate to human subjects is presented in figure 4.

In a preliminary report, Georgiewsky (330) stated that daily doses

of 0.5 gram of cinchophen for ten days increased the diuresis in human subjects. In normal animals, Starkenstein (331) observed that cinchophen did not increase the diuresis, but it increased the diuresis of epinephrine glycosuria. It merely accentuated an established diuresis.

**Albuminuria** The older clinicians generally reported the presence of albumin in urine after the administration of salicyl, but because of the confusion in the methods of testing for albumin, and the origin of the albuminuria, that is, whether febrile or renal, the question remained unsettled. The results of recent studies leave no doubt

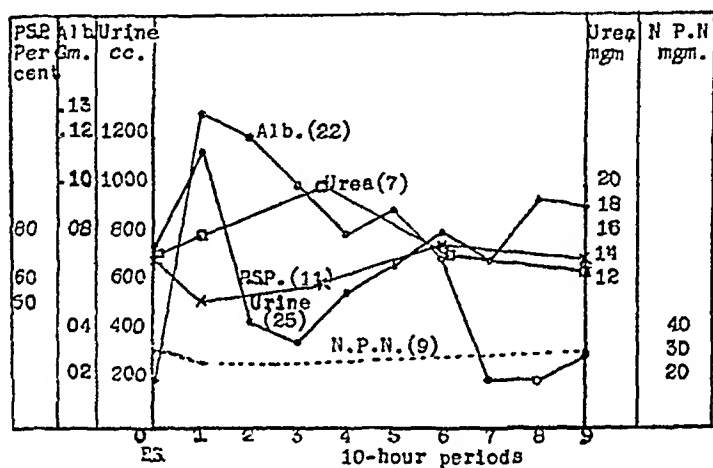


FIG 4 DIMINISHED RENAL FUNCTIONAL EFFICIENCY AND DIURESIS, AND MARKED ALBUMINURIA PRODUCED BY FULL THERAPEUTIC DOSES OF SODIUM SALICYLATE IN HUMAN SUBJECTS

*PSP*, means phenolsulphonephthalein, *Alb*, albumin in urine, *Urea-N*, urea nitrogen and *N P N*, non-protein nitrogen, milligrams in 100 cc of blood, *B S*, before salicyl and *A T*, at toxicity (symptoms of salicylism). The figures in parenthesis denote number of individuals.

that both salicyl and cinchophen cause albuminuria, and that it is of renal origin at least as far as salicyl is concerned. In adults, it appears that albuminuria is not demonstrable until about 3 grams of these drugs have been taken.

Among the first to report albuminuria after salicyl was Owen (332), who observed a temporary albuminuria in 78 per cent of his cases, and mere traces in 52 per cent, after salicylic acid and sodium salicylate. After therapeutic doses of sodium salicylate, v Ackeren (333) observed

albumin, blood and casts in the urine of patients, and produced hemorrhagic nephritis in rabbits by the administration of salicylic acid. From an examination of the urines of 33 patients with different clinical conditions, Luthje (334) found that the majority of the patients (febrile) showed the presence of albumin, hyaline, granular and epithelial casts, leukocytes and cylindroids. The urines were also examined before salicylate administration, and the dose given was usually 5 grams. A return to previous or normal condition occurred in from two to three weeks after the stoppage of the drug. Luthje ascribed these findings to a nephritis. Practically the same was observed by Kleinberger and Oxenius (335) in a large series of cases. The dose of the sodium salicylate ranged from 3 to 7 grams per day. Knecht, (336) however, differed with Luthje as to the renal origin of the albumin. He also found traces of albumin and occasional cylinders, but irregularly, and after doses of 0.3 gram in three or more doses these urinary changes did not occur. Brugsch (337) reported that when sodium salicylate was given in divided doses, i. e., 0.5 gram per dose until 5 grams were given per day, no renal irritation occurred. On the other hand, single doses of 5 grams each led to renal irritation in about 5 per cent of the cases. In Wiley's subjects (168) there was a general tendency to increased presence of casts and white blood-corpuscles, albumin excretion was unaffected. The data were few and incomplete. Examinations of urines from more than 100 patients, and from experiments on dogs and rabbits, led Ehrmann (158) to conclude that in only a few instances did albumin occur. The same was true in acute and chronic nephritis, but once an individual showed the presence of albumin in urine, this could be produced again by salicyl. After doses of 0.05 to 0.2 gram per kilo of acetylsalicylic acid, Chistoni and Lapresa (141) noted the presence of small quantities of albumin, casts and white corpuscles in the urine. Mumlock (338) denied the presence of albumin in different clinical conditions. In a statistical study by Hanzlik (298) of clinical cases with different disease conditions, and which received "toxic doses" of sodium salicylate, albuminuria appeared to be more common in the febrile than in afebrile conditions. Hence it was thought to be of febrile origin.

However, this deduction was not sustained in later studies on normal and diseased individuals by Scott and Hanzlik (329), Hanzlik

Scott and Thoburn (339) and Hanzlik, Scott and Reycraft (163). These studies were carried out as quantitatively as possible. Full therapeutic doses of sodium salicylate were administered, and a constant water intake was maintained throughout. The urine was examined qualitatively by the heat and acetic acid and ferrocyanide tests, and quantitatively by the gravimetric method of Folin and Denis (340) for the presence of albumin, and microscopically for leukocytes, casts, etc., before and after administration of the drug. The results are illustrated in figure 4 and may be briefly summarized as follows. The administration of sodium salicylate in full therapeutic doses invariably caused the appearance of albumin, white blood-corpuscles and granular casts or cast-like bodies in the urines of normal, rheumatic, convalescent, febrile and afebrile individuals. The albuminuria, therefore, was not of febrile origin. It was due directly to the drug, and a pre-existing albuminuria was aggravated. Quantitatively, the albuminuria reached its maximum at the time of symptoms of salicylism, then it gradually diminished and eventually disappeared, a trace of albumin persisting in those individuals who showed a trace of albumin before the administration of salicyl. These results agreed with those of Hanzlik and Karsner (341) on animals receiving corresponding doses of salicylate. Simultaneously, there were histological changes in the kidneys of the animals indicating nephritis, and a diminution in renal functional efficiency in both the animals and human subjects of these studies leaving no doubt that salicyl albuminuria is of renal origin. Rocco (161) found that 0.1 to 0.3 gram of salicyl salicylate per kilo of animal (dog and rabbit) caused the appearance of renal cells, leukocytes and albumin in urine.

As far as cinchophen is concerned, Hanzlik, Scott, Weidenthal and Fetterman (291) found this drug in full therapeutic doses to cause albuminuria and sometimes the appearance of casts and white blood corpuscles in the urine of the majority of seven individuals that were observed. The total dosage of cinchophen ranged from 4 to 19 grams. Doses of from 5 to 26 grams of neocinchophen gave variable results though albuminuria occurred in about one-half of the nine individuals that were observed. Albuminuria was claimed to be generally absent after small and large doses (up to 16 grams) of neocinchophen in a series of over 19 rheumatic and other patients reported by Barbour, Lozinsky and Clements (292).

*Bicarbonate on salicyl albuminuria* Glaesgen (342) claimed that, in human subjects, the administration of from 6 to 10 gram daily doses of sodium bicarbonate caused albuminuria to disappear after 3 to 6 gram doses of acetylsalicylic acid and the therapeutic effects were not lessened. Frey (343) claimed that large doses of salicylate in rabbits and dogs led to albuminuria, when the urine was rendered acid (by administering hydrochloric acid), and that albumin was absent in urine rendered alkaline by the administration of sodium acetate. On the other hand, Ehrmann (158) claimed that alkalinity had no influence on the excretion of albumin when albuminuria occurred, but he was not convinced that salicyl always caused albuminuria. The question was definitely settled in the negative by the observations of Hanzlik, Scott and Thoburn (339) and Hanzlik, Scott and Reycraft (163) on 7 human subjects receiving full therapeutic doses of sodium salicylate together with equal doses of sodium bicarbonate up to a total of 16 grams. There was no demonstrable influence on the albuminuria and the diminution in renal functional efficiency produced by the salicyl despite the high degree of urinary alkalinity persisting throughout.

*Renal functional efficiency* There is no doubt that salicyl and cinchophen increase the permeability of the kidney to uric acid, and possibly to urea, creatinine and chloride, though there is considerable uncertainty about the latter constituents of the blood. It appears that the uric acid effect is not obtained with doses of less than 3 grams of sodium salicylate. With medium and full therapeutic doses, an occasional individual responds with an increase in excretion of water (urine output). The cause of this increase is not known, it may be only a salt effect. However, in the majority of human individuals and in animals receiving full therapeutic doses of salicyl, the net result is a diminution in renal functional efficiency as indicated by the considerable reduction in diuresis discussed above, by a definite diminution in the excretion of phenolsulphonephthalein and by an increase in the urea nitrogen of the blood. This was shown in the studies of Hanzlik, Scott and Thoburn (339) and Hanzlik, Scott and Reycraft (163) on human subjects and of Hanzlik and Karsner (341) on animals. A summary of the results on human subjects is presented in the form of curves in figure 4, and shows quite plainly that during the decrease

in excretion of urine and phenolsulphonephthalein there was simultaneously an accumulation of urea in the blood. The non-protein nitrogen of the blood of the nine subjects studied was diminished somewhat during the increase in urea. It may be that the increase in the escape of the uric acid fraction of this nitrogenous portion was responsible for the change. However, in animals, the non-protein nitrogen and urea of the blood were both definitely increased. The uric acid was not estimated in any of these experiments. The changes in blood urea and in the excretion of phenolsulphonephthalein and water were demonstrable at the time symptoms of salicylism appeared, reached their maximum at the end of about 29 to 30 hours, and returned to their previous level at the end of about 60 to 70 hours after administration of the salicylate. Albuminuria was present simultaneously with all these changes in both the animals and human subjects. In the animals there were, in addition, definite indications of nephritis histologically, leaving, therefore, no doubt of renal injury from the salicyl.

Cinchophen, in full therapeutic doses, was found by Hanzlik, Scott, Weidenthal and Fetterman (291) to cause a definite diminution in the excretion of phenolsulphonephthalein together with albuminuria and other changes in the five human subjects that were studied. Neocinchophen, in full therapeutic doses, was more variable, causing a diminution in the excretion of phenolsulphonephthalein in about one-half of the 9 subjects that were observed, and who showed albuminuria at the same time. On the whole, the injury to renal function was somewhat less after cinchophen and still less pronounced after neocinchophen than after sodium salicylate in corresponding doses. In 8 patients receiving ordinary doses of cinchophen, Eisner (344) found the excretion of sodium chloride and total nitrogen decreased, both constituents returning to normal on withdrawal of the drug. In several cases there was later a compensatory increase in these urinary constituents. The uric acid in urine was always increased. An analogy between the action of cinchophen and calcium on renal function could not be established.

*Nephritis.* This has been demonstrated with salicyl in both animals and man. No studies with cinchophen have been reported. The occurrence of albuminuria, casts and sometimes hematuria, and the diminution in renal functional efficiency discussed above, suggest a

definite nephritis after salicyl. However, few human subjects receiving salicyl in therapeutic doses come to autopsy and, therefore, histological studies of human kidneys are practically non-existent. About the only reports on the human kidney are those of Vinci (345) and Wetzel and Nourse (273), the remaining three reports deal with animal kidneys.

Vinci (345) observed a toxic parenchymatous nephritis at necropsy of a man 45 years of age, who died 31 hours after the ingestion of 35 grams of sodium salicylate. There was marked congestion of all the renal vessels, particularly in the glomerular tuft, albuminous precipitate in the subcapsular space, interstitial hemorrhage, cloudy swelling and extensive necrosis of the tubular epithelium, most marked in the cortex, but as the necropsy was performed 2 days after death, and as the kidneys sent to Vinci were imperfectly preserved in alcohol, little importance can be attached to the histological changes. Experimenting with dogs, guinea pigs and rabbits he found that massive single doses, and frequently repeated large doses, led essentially to the same changes as he described in the human kidney. For the most part the drug was given by mouth, but in a few instances, intravenously and subcutaneously. He states that the lesions were most marked in dogs, less in guinea pigs, and least in rabbits. Luflye (334) gave repeated doses of sodium salicylate to 2 dogs, and both showed cylindruria, one showing albuminuria. The kidneys showed general congestion, interstitial hemorrhage, cloudy swelling, fatty degeneration, cast formation and, in the subcapsular space of the glomerulus, a homogeneous coagulum. Nephritis was ascribed to salicylate by Quenstedt (346) though on insufficient grounds. Hinzlik and Kirsner (341) made observations on the morphology and functional efficiency of the kidneys of dogs, cats and a rabbit receiving doses of sodium salicylate corresponding to the full therapeutic or so called "toxic," dosage used in human individuals, i.e. about 0.23 gram per kilo. In some cases only one dose was administered and in other cases repeated doses, the salicylate being usually injected hypodermically in 10 per cent concentration. In a few instances the drug was also given by mouth. The renal changes were the same as when the drug was given hypodermically. As a rule the animals were observed for 2 to 3 days before the experiment was begun, since they



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almost invariably showed some evidences of albuminuria. Studies of changes in the albuminuria and fixed elements in urine and in the urea and non-protein nitrogen of the blood were made at the same time. Then the animals were killed, necropsy performed and kidneys at once placed into a fixing solution. Besides the albuminuria and diminution in renal functional efficiency which occurred in all of the

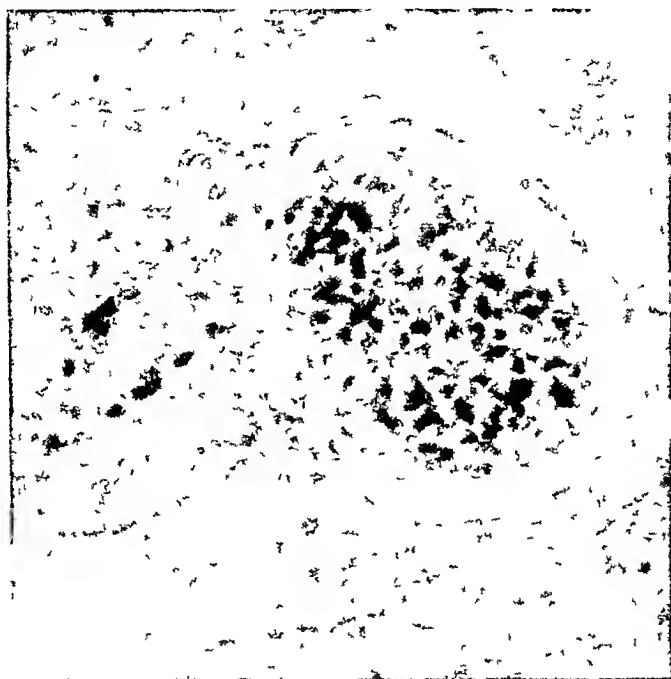


FIG 5 SECTION OF DOG KIDNEY ILLUSTRATING TUBULAR NEPHRITIS FOLLOWING HYPO-  
DERMIC INJECTION OF SODIUM SALICYLATE (0.3 GRAM PER KILO)

Shows slight involvement of the glomerular tuft, which, although not enlarged, is richly cellular and devoid of blood. The tubular epithelium shows cloudy swelling and the lumina contain granular albuminous precipitate.

eleven animals studied and were described above, there were definite morphological changes in the kidney. The renal lesion varied in severity from simple cloudy swelling of the epithelium of the proximal convoluted tubule to extensive cloudy swelling of all the cortical parts of the tubules, associated with an acute intracapillary glomerulitis, the latter process being denominated as an acute tubular nephritis. These changes agree essentially with those of Vinci, but, contrary to

his claim, there were no material differences in the susceptibility of dogs and cats. Vinci's failure to find the more marked glomerular lesion was probably due to the fact that most of his animals died or were killed after only 7 or 8 hours. Figure 5 illustrates the changes in a dog kidney from the experiments of Hanzlik and Karsner. The recent report of Tocco-Tocco (347) on renal changes from salicyl is in essential agreement with the results just given, the most serious alterations being in the glomeruli, tubules and vasi. On direct treatment with ferric alum these regions gave the most marked color reactions for salicyl, from which Tocco-Tocco concludes that the salicyl accumulates in the regions most markedly affected morphologically.

In their case of fatal poisoning in an infant 21 months old who drank about 10 cc. of oil of wintergreen (methyl salicylate), Wetzel and Nourse (273) found cloudy swelling and fatty degeneration in the tubular portion of the renal cortex, but the glomeruli were unaffected. The kidney parenchyma showed a generalized hyperemia and hemorrhages. The urine showed a faint trace of albumin and occasional hyaline casts.

The only report on cinchophen is that of Nicolaier and Dohrn (28), who state that a rooster which had received 44 grams of the drug in 66 divided doses showed no histological changes in any of the organs, but no details are given.

### *Salicyl edema*

*Systemic* This was described by Hanzlik, Scott and Reycraft (163), who observed it in 9 human subjects after administration of full therapeutic doses of sodium salicylate. It is characterized by an increase in body weight demonstrable about 20 hours after the beginning of administration of the salicylate and persists until the salicyl excretion is completed, that is, till the end of about 80 hours, or 3½ days. Simultaneously there occur a marked diminution in diuresis, a diminution in phenolsulphonephthalein excretion, an accumulation of urea in the blood and albuminuria, all of these elements returning to their previous levels with the disappearance of the edema. Since the diminution in renal functional efficiency generally makes its appearance before an actual increase in body weight is demonstrable, and later coincides with it, it seems that the renal factor plays an

important rôle in the production of the edema. The retention of water occurs mainly in the tissues, since no dilution of the blood is demonstrable by hemoglobin estimations. Diaphoresis may modify the degree of the edema, but it is not modified by the administration of bicarbonate together with salicylate in large doses (up to 16 grams) and sufficient to maintain the urine alkaline. Swift (348) states that he has not observed as marked changes with respect to edema and renal injury as have just been described, but does not deny their

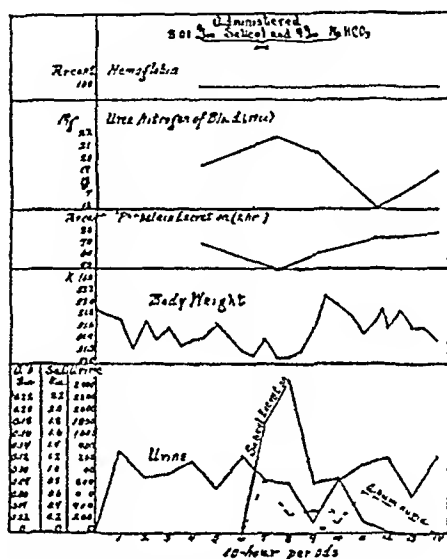


FIG 6 SYSTEMIC EDEMA AFTER A FULL THERAPEUTIC DOSE OF SODIUM SALICYLATE IN A HUMAN SUBJECT (PATIENT 28)

Shows increase in body weight, accumulation of blood urea, diminished excretion of phenolsulphonphthalein, diminished output of urine, albuminuria, excretion of salicyl and unchanged hemoglobin

occurrence with large doses of the drug. The typical phenomenon, including the various changes in blood, urine salicyl excretion and body weight, is illustrated in figure 6.

**Pulmonary edema** Chatin and Guinard (349) produced pulmonary edema together with increases in salivary, bronchial, nasal and digestive secretions in animals by injecting methyl salicylate (0.025 gram in dogs and 0.047 gram in rabbits) intravenously, the circulation was only moderately affected, and respiration stopped before the heart. Chanoz and Doyon (350) produced the edema in dogs by injecting

amylsalicylic ether intraperitoneally or intravenously (0.5 to 0.8 gram per kilo), death occurred from arrest of respiration and convulsions. According to Teissier and Guinard (351), the cause of the edema was not due to an increase in pulmonary arterial pressure because the pressure was only slightly increased in curarized animals receiving artificial respiration and injections of the ester. That is, mechanical difficulties alone were insufficient, although they facilitated the occurrence of lung edema. Additional important elements were vasodilation and intoxication. These authors injected from 2 to 7 cc. into the jugular veins in 20- to 24-kilo dogs. The vascular changes might be expected to occur from an irritant volatile oil such as methyl salicylate. Apparently the acute pulmonary edema of methyl salicylate differs as to cause from the systemic edema of sodium salicylate, although it is possible that the vessels are also affected in the latter type.

*Local edema of ears* The edema action of salicyl esters might be expected to hold for other regions besides the lungs. This was demonstrated by Dreser (357), who applied mesotan (methyl oxy-methyl salicylate) directly to rabbit ears. The swelling of the ears was determined by measuring the volume of water displaced on immersion of the organs into cylinders. The application of 1 gram mesotan to an intact ear caused it to increase 14 cc. in volume at the end of 22 hours, and to 18 cc. at the end of 28 hours. It took 4 days before the ear returned to its original size. Mesotan in oil did not cause as much swelling owing apparently to competition of the lipid solvent with the ear. The ear experiments indicate the basis for the use of salicyl esters locally as irritants. As compared with methyl salicylate, spirosal (monoglycol salicylate) and possibly ethyl salicylate are less irritating. All of these esters are useful as counterirritants.

### *Circulation*

Small therapeutic doses of salicyl and cinchophen do not affect the circulation demonstrably except in susceptible individuals who respond with some acceleration of the pulse and consciousness of the precordia. Full therapeutic doses cause some depression though this is comparatively unimportant, while large and toxic doses definitely depress and finally paralyze the circulation in the manner of the

coal-tar derivatives in general. However, clinical investigations with modern methods are practically non-existent. The following summary contains mainly the results of studies on animals and excised organs.

*Blood pressure* After intravenous injection of either salicylic acid (0.023 gram) or its sodium salt (0.08 gram) in rabbits, Kohler (353) observed a fall of blood-pressure after section of the vagi, depressors and cervical cord, and this was proportional to the dose. No such effects were observed when the drug was given by mouth, but in dogs gastric administration was followed by a fall of blood-pressure, with retardation of the pulse. Later Kohler (354) found that intravenous injection of doses from 0.5 to 0.75 gram in dogs resulted in a rise of blood-pressure with retardation of the pulse and respiration, but this was due to asphyxia, since in curarized animals with artificial respiration the effects were those of depression. Moreover, further injections caused the blood pressure to fall progressively and the pulse was slowed. Kohler denied the claim of Danewski (355) that salicyl stimulates the vasomotor center and the vagus, acting like digitalis. Oltramare (356), also having obtained a rise in arterial pressure with moderate doses, concluded it to be of central vasomotor origin. Clinically, Maragliano (357) noted usually an elevation in the pressure, never depression.

According to Chatin and Guinard (349), intravenous injection of methyl salicylate, in absolute doses of 0.025 gram in dogs and 0.047 gram in rabbits, caused a marked but transient fall of blood pressure (carotid) followed by a fleeting rise, followed later by a fall with acceleration of the pulse. The cause of these changes was not determined, but it was stated that other methods of administration did not affect the circulation. The action on pulse was feeble and unimportant with small doses of the ester. Essentially the same effects of methyl salicylate on blood pressure were observed by Teissier and Guinard (351).

Intravenous injections of large doses of cinchophen in cats and dogs cause stimulation of the vagus and vasomotor centers followed by depression with corresponding effects on the blood pressure (230). Using "leukotropin," a mixture of cinchophen and hexamethyleneamine, injected intravenously in a dosage corresponding to about 0.2

gram cinchophen in rabbits, Ullmann (283) observed a fleeting fall of blood pressure with slowing and increase in volume of the heart. This was prevented by large, but not by small, doses of atropine. The fall of blood pressure appeared to be due to cardiac slowing from vagus stimulation. Section of the vagi and decerebration did not prevent the action, and therefore the vagus stimulation was peripheral. This agreed with parasympathetic stimulation of the intestine. Epinephrine antagonized the circulatory action of cinchophen. In man, there were no effects on blood pressure and the heart from the intravenous injection of 10 cc of the mixture, containing about 1 gram of cinchophen. On the other hand, Starkenstein (320) claims that the lowering of blood pressure caused by intravenous injections of minimal effective doses of cinchophen in cats, dogs and rabbits is not of vagal origin.

*Intact heart.* As a rule, there is no effect with small, but depression occurs with large, doses of salicyl and cinchophen. In frogs, Istomin (358) and Istomin and Weliky (359) observed at first a slowing of the pulse, later an acceleration after small doses. This only returned to normal in 60 to 100 minutes if the spinal cord was not cut. The heart stopped in incomplete systole and was unaffected by atropine or electrical stimulation. Blanchier (97) observed an increase in rate and strength of the heart beat during a small rise in blood-pressure which was probably of central origin. With increase in dosage, this was followed by arrhythmia, irregularity, diminution in strength of pulse with sudden stoppage of the heart and cessation of respiration. In guinea pigs, Houghton (77) found ethyl salicylate in doses of about 0.0015 gram per gram body weight to slow the heart, large doses producing cardiac standstill. This action was presumably on the cardiac muscle direct. The effects of methyl salicylate (0.0007 gram per gram body weight) were more pronounced on account of its greater toxicity. The results of Borrisow (360) appear to be in accord with those of others.

With sodium cinchophen injected intravenously, Starkenstein (320) observed a temporary slowing with increase in amplitude of the pulse in rabbits, but not in cats and dogs. He denies a vagus type of pulse from this drug. Essentially the same changes in rabbits were obtained by Ullmann (283) with "leukotropin," but he interprets the mechanism



as a "vagus shock," and states that Starkenstein's injections resulted frequently in thrombosis

Clinically, Sée and Lahalle (361) observed no change in pulse-rate and rhythm with comparatively small doses of sodium salicylate. With small as well as larger therapeutic doses, Maragliano (362) noted an increase in the strength of the heart beat, and the systolic pressure reached its maximum in 2 hours and returned to normal in 3 to 5 hours, the normal diastole usually being accentuated. Doses of from 4 to 19 grams of cinchophen were found by Hanzlik, Scott, Weidenthal and Fetterman (291) to slow the pulse rate about 25 per cent in both febrile and afebrile subjects (eight). The slowing, therefore, was not the result of antipyretic action. Neocinchophen also slowed the pulse in 4 febrile subjects.

*Perfused heart.* The isolated heart is not readily poisoned by salicylate as indicated by the fact that rather high concentrations are necessary for definite effects. Such concentrations are much higher than the concentration of about 0.02 per cent occurring in blood after full therapeutic, or clinical "toxic," doses.

Faval (363) found low concentrations ineffective for the isolated frog heart, high concentrations paralyzed. Friedrichsen (128) noted that concentrations of from 0.04 to 0.05 per cent of sodium salicylate in Locke's solution, and of 0.2 per cent in blood, were necessary to cause stoppage of the perfused frog heart. Lower concentrations reduced the rate and strength of the heart beat. In the living frog, a concentration of 0.4 per cent sodium salicylate in the blood stream was necessary to cause stoppage. In the intact rabbit a concentration of 0.12 per cent of sodium salicylate had no effect, but with higher concentrations the pulse was slowed, blood-pressure fell and the heart stopped. The excised and perfused heart was depressed by a concentration of 0.12 per cent. Death occurred when the concentration of salicylate reached 0.13 per cent in the blood after administration of the drug by mouth, but 0.06 and 0.08 per cent concentrations in the blood were endured for 24 hours without death. Friedrichsen noted also that beef and rabbit serums always contained more salicylate than the erythrocytes, the proportion in serum to whole blood being 1.2 to 1. Salant and Johnson (364) found that perfusion of the isolated frog and turtle hearts with a concentration of 1:2000 sodium salicylate had no

effect or stimulation, 1 1000 at the end of 10 to 15 minutes caused considerable depression, and there was a slight improvement sometimes on discontinuation of the perfusion, but complete recovery was not observed, 1 500 and 1 250 caused still greater depression Okushima (365) reports that the action of salicylic acid and its sodium salt on the heart resembles that of other aromatic acids and their salts, and suggests that the depressant action of salicylates is due to liberation of the acid by metabolites given off by excised organs, especially as an effect is more rapidly obtained with an organ in activity than when it is at rest However, this implies a much higher degree of acidity in tissues than probably exists

In a later report, Okushima (366) stated that the esters of various aromatic acids have a more pronounced effect on the isolated heart than the corresponding sodium salts of their acids, but on hypodermic injection in mice the salts were more effective than the esters The latter would seem to be a matter of solubility In the experiments of Salant and Johnson (364), heart block occurred in 2 to 3 minutes after perfusion of the isolated frog heart with concentrations of 0.7 per cent or less of the methyl and ethyl salicylates, the effect was promptly removed with Ringer's solution Acetylsalicylic acid, in concentrations of 1 4000 to 1 2000, caused marked depression, but when the pH of the solution was maintained at 7.4 or 7.5 stimulation occurred, and, therefore, this derivative was less toxic than the sodium salt of salicylic acid Mendenhall and Camp (367) observed that acetylsalicylic acid had a stimulant effect on the intact and perfused frog heart as indicated by lowering of the threshold to electrical stimulation, the action of the drug being direct and not due to paralysis or inhibition of the vagi The dosage in frogs was 0.25 mgm per gram body weight Injection of doses comparable to the therapeutic in cats accelerated the heart and increased the blood pressure independently of the vagi They concluded that the drug is depressant to the heart only in concentrations much higher than would be likely to occur even after large doses Using Williams' perfusion apparatus and defibrinated ox blood, Dreser (11) estimated the cardiac output and work of the frog's heart during perfusion with 0.2 per cent sodium salicylate This salt left the force unchanged, but reduced the pulse volume as compared with a control solution, while 0.25 per cent

acetylsalicylate increased the work through an increase in pulse volume though the force remained unchanged. These results were essentially similar to those of Salant and Johnson.

Ullmann (283) observed that perfusion of the isolated frog heart with "leukotropin" resulted in slowing of the rate and diminished systole, in other words, direct depression. The effects were antagonized by calcium. Rotter (255) claims paralysis of cardiac nerves in the frog's heart treated directly with cinchophen, the heart usually stopping in systole, but this seems entirely out of line with the results of Ullmann and of Starkenstein discussed above. Hydroatophan, according to Pohl (368), does not possess the action of cinchophen on the amphibian heart, but causes intense spinal and peripheral stimulation resulting in tetanus and fibrillary contractions.

The main criticism of the majority of reports on the perfused heart is the failure to take into consideration the changes in the perfusion fluid resulting from the addition of cinchophen and salicyl and their derivatives. These changes consist essentially of the alterations in reaction (pH) from cinchophen and the salicylic and acetylsalicylic acids, which would reduce the alkalinity, and from the sodium salts of the compounds, which would increase it, since they are salts of relatively weak acids. In the case of "leukotropin," the presence of hexamethylenamine might alter the action of cinchophen. In other words, the cardiac effects observed may have been due to pH changes, etc., rather than to the drugs themselves.

*Blood vessels* These tend to be relaxed by all concentrations. Dreser (11) found the vessels of frogs with cord destroyed relaxed on perfusion with sodium salicylate and sodium acetylsalicylate, the concentrations were not stated. Dilatation of the peripheral vessels from sodium salicylate in higher animals was observed by Wiechowski (369). The intracranial vessels were constricted, but the homologues, benzoic and p-oxybenzoic acids and acetylsalicylic acid and methyl salicylate had no such action. In his direct observations of capillaries in the frog's mesentery, Ikeda (280) saw no depression of the circulation here from the injection of cinchophen, while quinine depressed. A relaxation of vessels from salicyl and cinchophen might be expected as was found to be the case with a variety of aromatic substances by Kondo (370). The action is on the smooth muscle itself and results in

paralysis with concentrations which oppose and prevent the actions of barium and epinephrine. In experiments with excised vessels themselves or those of excised organs, it is necessary to keep in mind the changes in pH of the fluid just as in the case of the isolated heart. Unfortunately, this was not the case in the few reports discussed. Nevertheless, the results generally agree with those of injection experiments which are not subject to the same local changes.

### *Respiration*

Ordinary therapeutic doses of salicyl and cinchophen do not appreciably affect the respiration, but full therapeutic doses tend to accelerate and deepen it. Toxic doses depress and finally paralyze. The early effects appear to be of circulatory origin, since they occur at a time when the pulse is slowed and the blood-pressure tends to fall. Dosage is an important factor, but clear cut analyses are still lacking, and the available reports are somewhat contradictory.

After gastric administration of sodium salicylate and salicylic acid in dogs, a slowing of the respiration was noted by Kohler (353, 354). In guinea pigs and dogs, Blanchier (97) noted an acceleration at first, followed by interrupted respiration, dyspnea and death from asphyxia. Practically the same was observed by Chirone and Petrucci (195). Danewski (355) claimed that, if the vagi were cut before injection of the salicylate, the respiration was only slightly accelerated. Thus then returned to the same rate as in the control untreated animals with sectioned vagi, the drug, therefore, acting independently of the vagus mechanism. The marked increase in respiration and air hunger after hypodermic and intravenous injection of sodium salicylate in animals were found by Hurlley and Trevan (274) to be similar to those of acetoacetate and ethyl acetone, enol compounds, which reproduce the symptoms of diabetic acidosis. Small doses of ethyl salicylate in guinea pigs at first slowed then accelerated the respiration, according to Houghton (77), large doses paralyzed. Houghton also observed that no absorption of this ester took place by the respiratory passages. In dogs and rabbits, Chatin and Guinard (349) observed constant effects after intravenous injection of methyl salicylate, namely, acceleration of respiration and dyspnea, which increased with the degree of poisoning, and finally the respiration stopped before the heart. In

these experiments the circulatory changes were relatively unimportant

Clinically, Deseille (287) reported no change in respiration after therapeutic doses of salicylate. Ullmann (283) states that cinchophen, in the form of "leukotropin," increases the asthmatic attacks in man.

### *Skeletal muscle and nerve*

The sodium salts of salicylic acid and cinchophen have no demonstrable direct effects on skeletal muscle, but the free acids depress. The convulsant action after administration is analogous to that of phenol and entirely central in origin. In the intact frog, Livon (371) reported that sodium salicylate caused first an increased and later a decreased irritability. Acceleration of rigor mortis was reported by Blanchier in 1879 (97), and this is characteristic of convulsants in general. Recently, Schuller (322) demonstrated the absence of toxic action from the sodium salts of salicylic acid and other aromatic acids on excised frog muscle. When carbon dioxide was passed through the solutions of the sodium salts, the toxicity increased with the increase in lipid solubility of the acid liberated, and, therefore, in accordance with physical-chemical behavior. The ultimate effect, however, was determined by the chemical constitution of the acid. These results agree, in general, with those of Thienes (323) on smooth muscle, who found that the alterations in functional response were produced only by the lipid soluble salicylic acid and not by the sodium salt. Schuller (372) finds, also, that sodium salicylate, sodium cinchophen, and sodium cumarate can remove the actions of caffeine and veratrine (contracture) on skeletal muscle. He thinks the antagonism to these alkaloids rests on the same basis, and claims it is rather uniform for all agents with the hydroxyl group in the ortho position, including the antagonists tried. The presence of calcium hinders the antagonism. A definite explanation of the antagonism is not at hand, but in the case of the caffeine-salicylate antagonism, it seems the caffeine is removed through the formation of the complex, though very soluble, caffeine sodium salicylate. The same is suggested as the explanation of the veratrine-salicylate, and possibly veratrine-cinchophen, antagonism.

Salicyl and cinchophen do not act on peripheral nerve structures.

They do not produce local anesthesia. The alleviation of pain locally, claimed by some for methyl salicylate, especially on joints, is probably due to a counter-irritant action, although it is true that Dreser (352) demonstrated some depression of reflexes from frog's skin treated with the undiluted ester. There was some prolongation of the reflex time elicited by electrical stimulation of the skin. A saturated solution of the ester in water, however, was ineffective. The analgesic action of these drugs is mainly central, and analogous to that of other coal tar derivatives such as acetanilide and antipyrine. The depression is marked enough to relieve the pains of neuralgia and arthritis and headache, but not enough even with full therapeutic doses to permit minor operations. A mild hypnotic action is experienced by some individuals, especially with acetylsalicylic acid, but this does not compare with the activity of such hypnotics as morphine, bromide, barbital, etc. Saturated vapors of methyl salicylate were found by Dreser (362) to completely narcotize mice, depression was still present at the end of 20 hours, complete recovery occurred on the third day. Fish were narcotized in 5 minutes by a concentration of 0.003 per cent in water, but not by an equal concentration of mesotan, the latter being effective, however, in 2 minutes when twice the concentration was used.

### *Uterus*

*Emmenagogue action.* After large doses of salicylates, uterine hemorrhages, miscarriages and premature births have occurred. These have usually occurred during the treatment of rheumatic fever and it is probable that the febrile condition was responsible in part at least. Strong menstrual and abortive effects due to salicylates have been reported by Mittos (373). According to Pullmann (374), Schuchardt (375), Wacker (376) and Linhart (377) hemorrhages from the mucosae occur in some individuals after taking salicyl. It has been suggested by Binz (378) that this may be the basis of frequent or excessive menstruation, and of miscarriage or premature birth, after salicyl.

*Excised and intact rabbit uterus.* The occurrence of abortion seemed to be supported by Binz's experiments (378) on pregnant rabbits. Five out of 15 rabbits aborted after doses of salicyl which had no other action. Binz left the mechanism unexplained, but advised

caution in the use of the drug in cases with a tendency to miscarriage or hemorrhage Gunn and Goldberg (379) observed the effects of sodium salicylate on the motility of excised and intact pregnant and non-pregnant uteri of rats, guinea pigs, cats, and rabbits They demonstrated a definite stimulating action The action was not powerful, on the isolated uterus it was only half as strong as sodium carbonate and about one-fortieth as strong as quinine A concentration of 1/1000 of sodium salicylate added directly to the excised strips always stimulated as indicated by an increase in tonus, or rate, or induction of movements in a previously quiescent uterus Strengths of 1/2000 and less had some stimulating action, while 1/500 caused a primary stimulation followed by depression The effects were reversible and probably muscular Since the concentration of sodium salicylate in blood after full therapeutic doses is about 0.024 per cent, and at least 0.05 per cent was necessary in Gunn and Goldberg's experiments to cause slight stimulation, it does not seem that the muscular action alone is responsible for abortions occurring in rheumatic fever Gunn and Goldberg noted some fleeting stimulation of the intact uterus after doses up to 0.2 gram per kilo in nearly two-thirds of their 21 experiments The effects consisted of an increase in rate or amplitude of contractions In over a third of the experiments salicylate had no effect on the uterus When the drug was given in divided doses, as it is in rheumatism, the stimulation was not obtained From their results, Gunn and Goldberg concluded against the importance of salicyl as an abortifacient unless the uterus is specially sensitive, and suggested that abortion occurring in rheumatic fever is the result of the fever, or it may arise in some cases from hemorrhage into the uterus This seems correct, but it is still possible that the human uterus is more sensitive than the animal uterus to both the permeability and muscular actions of salicyl, or that abortion is caused indirectly through effects of salicyl on the fetus, for instance, by inducing respiration and causing struggling and death Therefore, Binz's advice is still valuable

#### *Auditory organs*

Tinnitus aurium is one of the symptoms of salicylism, or cinchonism, occurring after full therapeutic doses of salicyl and cinchophen in

human subjects. In rabbits, mice and guinea-pigs poisoned with sodium salicylate, disturbances in the auditory apparatus do not occur from hemorrhages in the labyrinth as thought by Kirchner (380), but rather as according to Blau (381) and Haake (382), who also made experimental studies and found that there is injury to ganglion cells in the spiral ganglion, and particularly in the vestibular ganglion, similar to that produced by quinine as observed by Wittmaak (383). This injury consists of an alteration in the staining properties of the nerve cells, alteration in the distribution of the Nissl bodies, partial disappearance and sometimes destruction of the entire nerve cell. These changes are not characteristic of salicylates. They can also be produced by asphyxia, strangulation, convulsions and such drugs as arsenic and strychnine. Lindt (384) observed no degenerative changes in the auditory nerve after administration of salicylate and quinine, and states that it is as yet unknown where these drugs act to produce the ear symptoms. Congestion may be responsible for them, for dilatation of cerebral vessels after salicyl and related drugs has been reported by Berezin (385) and Wicchowski (369).

Tinnitus aurium and other symptoms of salicylism occurred in only 20 per cent of the subjects receiving neocinchophen as compared with the majority or 65 per cent of those receiving cinchophen in the series of Hanzlik, Scott, Weidenthal and Fetterman (291). This did not seem to be a matter of dosage. Neocinchophen, therefore, probably has some advantage in this respect over the salicylates and cinchophen. No experimental studies of the ear have been made with these drugs.

### *Sweating*

Sweating occurs after small and full therapeutic doses of salicyl and cinchophen. This is sometimes quite marked with the relatively small doses of acetylsalicylic acid used in the treatment of colds. In febrile conditions it is usually more marked than in the afebrile, but the sweating may be so marked after full therapeutic doses in the afebrile as to reduce the body weight. This was observed by Hanzlik, Scott and Reycraft (163). Justi (386) observed that a profuse sweat takes place in fifteen minutes after administration of salicyl in fever, and Goldammer (387) and Ewald (76) noted that the perspiration may be so marked as to cause exhaustion. The doses of salicyl em-



ployed by Hare (cit H C Wood (388)) in a clinical study of this question did not produce sweating. The diaphoretic action may be connected with the peripheral vasodilation caused by these drugs, and, in fever, the fever has probably an added influence. The sweating is of course important in the antipyretic action of the drugs.

### *Temperature and heat regulation*

Salicyl and cinchophen are prompt and efficient antipyretics. In 1874, Kolbe (29) first suggested an antipyretic action for salicyl on the basis of certain other pharmacological resemblances to quinine, which however had nothing to do with a temperature action, and Buss (389) demonstrated its antipyretic action in 1875. Formerly the antipyretic action was attributed to depression of the heart and respiration, but this was incorrect because the temperature action occurs before cardiac depression is demonstrable, the latter requiring much higher concentrations than occur in the body after therapeutic doses. Salicyl undoubtedly dilates the peripheral vessels including those of the skin, probably through central depression, and this together with the accompanying sweating, at least in fever, suggests the probable mechanism of the antipyresis. It was seen that protein metabolism is somewhat increased, if anything. Depression of metabolism (heat production), therefore, is excluded as indeed is indicated by the results of various studies of this feature. The mechanism, therefore, appears to be similar to that of acetanilide and antipyrine, and consists essentially of increased heat dissipation. Whether it resembles or differs from quinine it is difficult to say at present because the long-accepted depressant action of quinine on metabolism has been seriously questioned by Hardikar (390). It seems to be generally agreed that quinine is a more powerful antipyretic than salicyl and cinchophen. Sweating is not indispensable to the antipyretic action, since perceptible sweating does not always occur during the antifebrile action, and again marked sweating occurs after salicyl in normal individuals without as a rule a lowering of body temperature. Although the following summary shows that as yet there is not a complete agreement on the effects of salicyl on normal temperature, the tendency of the results is toward the negative side, animals being more variable than man as might be expected.

*Normal animals* Practically negative results with salicyl on body temperature in normal animals have been reported by the following investigators, Buss (389), Furbringer (53), Barbour and Herrmann (391) in dogs, Morinaka (392) in dogs and rabbits, and Dreser (11) in rabbits. The reason for the negative effects in the experiments of Barbour and Herrmann was the absence of blood dilution, which, however, occurred in febrile dogs. The blood dilution appeared to be dependent on the increase in concentration of blood sugar. The average maximum increases in sugar after acetylsalicylic acid and sodium salicylate were 25 and 48 per cent, respectively, in the normal, and from 44 and 50 per cent, respectively, in the febrile dogs. The dosage of sodium salicylate was 0.25 gram, and of acetylsalicylic acid 0.5 gram, per kilo. Slight temperature increases after both drugs were observed in some of the dogs, thus preventing the blood dilution, if anything, and therefore favoring the theoretical explanation. However, the increases in blood sugar in the afebrile and febrile dogs were so nearly alike that the presence of hydremic plethora in one group of dogs and not in the other seems rather paradoxical, especially in view of the claims that the increase in dextrose is one of the chief factors in the blood dilution. From this it seems that the absence of temperature changes after salicyl in normal dogs has some explanation other than the absence of blood dilution. In his study of sodium salicylate, acetylsalicylic acid, quinine, and some other antipyretics on the excretion of nitrogenous constituents in dogs and rabbits, Morinaka found only insignificant variations in these products, and, therefore, no important depression of tissue metabolism. Dreser also found acetylsalicylic acid to be negative in rabbits.

On the other hand, several investigators have demonstrated definite effects on normal temperature in animals. Churone and Petrucci (195) found small doses of sodium salicylate to lower, and large doses to increase, the temperature in dogs and rabbits, these latter results agreeing with certain ones of Barbour and Herrmann who used doses corresponding to the full therapeutic. Using a special metal cannula through which hot and cold water were passed for stimulation of the heat and cold centers in the rabbit brain, Hashimoto (393) demonstrated a diminution in the irritability of the heat centers after administration of sodium salicylate and antipyrine. The application of

heat alone by this method results in an increase in body temperature and flushing of ears, shivering being absent, while the opposite effects occur on the application of cold. Salicyl diminished the responses to application of heat, and the application of cold removed the diminution. Morphine diminished the responses to both heat and cold, indicating a difference from salicyl, which appeared to have a specific action on the heat centers. These results indicate some central depression from salicyl.

An increase in heat dissipation amounting to 43.3 per cent together with an increase of 39.6 per cent in heat production in normal dogs was reported by Wood and Reichert (394) after doses of from 1 to 5 grams of sodium salicylate. Increased dissipation was regularly observed by Stuehlinger (395) in guinea pigs receiving sodium salicylate. Livon (396) found the carbon dioxide production generally increased in guinea pigs, turtles and frogs with sodium salicylate. In the experiments of Singer (213) on rabbits, 0.3 gram acetylsalicylic acid by mouth decreased the oxygen consumption 17 and 14 per cent, while a "toxic" dose of 0.9 gram increased it 9 per cent. In an extensive and controlled study of the temperature and heat in mice according to modern methods and with the aid of a thermoelectric needle, Yoshinaga (397) observed that 0.3 gram per kilo of sodium salicylate or acetylsalicylic acid orally lowered the temperatures of the peritoneum and the skin of the back. The reduction amounted to about  $0.2^{\circ}\text{C}$ . in the majority of mice with a return to normal at the end of one hour. A detailed study of the mechanism of temperature reduction in a mouse of 12 grams kept at room temperature ( $18^{\circ}\text{C}$ ) showed that during a reduction of  $2.8^{\circ}\text{C}$ , there was a greater reduction, i.e., 17.3 per cent, in heat formation (carbon dioxide per hour) than in heat dissipation, i.e., the calories per hour were reduced only 2 per cent. The total calories were reduced from a normal of 200.2 to 196.1 after the salicyl compounds. The distribution of the caloric reduction was as follows: by evaporation, from 16.3 to 15.5, by air, etc., from 0.7 to 0.6, and by radiation and conduction from 183.2 to 180.0. The effects of salicyl were similar to those of other coal-tar derivatives, namely, antipyrine and phenol. In their study of antipyretics on tissue respiration by means of succinhydrogenase, Nitzescu and Cosma (398) observed that sodium salicylate stood next to quinine as a depressor of oxidative

processes Yamamoto (399) reported that although acetylsalicylic acid possessed a greater antipyretic efficiency than salicylic acid, yet no appreciable difference was found in the combining efficiency of the two compounds with brain tissue

In rabbits and dogs, the hypodermic injection of cinchophen was found by Starkenstein and Wiechowski (230) to cause some lowering of normal temperature. The action appeared to be both central and peripheral. Central depression was indicated by a diminution in the irritability of the respiratory center, and by a reduction of central vagus stimulation and of asphyxial reactions. The peripheral action was apparently concerned with vasodilation. In some later experiments, Starkenstein (400) found that cinchophen did not lower the temperature of decerebrated and warmed rabbits, but lowered it when the rabbits were removed from the warming box. From this it was concluded that the temperature lowering action of cinchophen must be central, the depression or paralysis of the heat centers impairing heat regulation similarly to the action of antipyrine. Arguing from certain experimental results, namely, that withdrawal of calcium causes fever and increases the irritability of the sympathetic nervous system, Starkenstein sees in this an analogy to the action of cinchophen and some further considerations incline him to the view that the actions of cinchophen are fundamentally concerned with the sympathetic nervous system. However, several other actions do not fit perfectly into this analogy. On the other hand, the lowering of temperature after "leukotropin" (a solution of cinchophen in hexamethylenamine) in rabbits is attributed by Ullmann (283) to a stimulation of the parasympathetic nervous system. It is claimed that the respiratory center was paralyzed and the pupil constricted simultaneously, the constriction being relieved by atropine. The claims that cinchophen exerts its effects on body temperature through the sympathetic and parasympathetic nervous systems do not seem well established. There is no reason to believe that cinchophen acts differently from salicyl on body temperature, but further and more critical analysis is desirable.

What appears to be a potentiation of cinchophen on temperature in rabbits has been reported by Dittrich (401). Weak and inactive doses of cinchophen caused a marked lowering of temperature when the

the case with the afebrile and practically normal individuals of Hanzlik, Scott and Reycraft (163)

Whether the changes in blood sugar and dilution are of sufficient magnitude to explain the action of antipyretic drugs is a matter that can not be considered further here, but would seem to merit further study before it can be accepted without question. The blood changes may be only incidental to the temperature changes. However, anyone interested may consult a recent review of the subject by Barbour (410)

Using dogs rendered febrile with injections of typhoid, paratyphoid and *B. coli* vaccines, Barbour and Lozinsky (299) compared the antipyretic and toxic effects of acetylsalicylic acid, cinchophen and neocinchophen. Acetylsalicylic acid acted more quickly than cinchophen and neocinchophen. However, neocinchophen was the least toxic of all. The ratios of the minimal antipyretic to the minimal lethal doses

$$\frac{C}{T} = \frac{\text{minimal antipyretic dose}}{\text{minimal lethal dose}}$$

were estimated to be as follows: neocinchophen  $\frac{1}{150}$ , cinchophen  $\frac{1}{63}$  and acetylsalicylic acid  $\frac{1}{25}$ . Accordingly, the therapeutic range of neocinchophen was thought to be much greater than that of cinchophen and acetylsalicylic acid. Unfortunately, however, the febrile temperature in dogs with vaccine fever tends to recover spontaneously rather promptly, and frequently additional injections of the vaccine fail to produce fever. In other words, the error in such experiments may be considerable, and the antipyretic action due to spontaneous recovery and not to the drug administered. Extensive series of experiments with adequate controls are desirable in making comparisons of the efficiency of different drugs. Since neocinchophen is so poorly absorbed (discussed under absorption) from the alimentary tract, it is conceivable that the administration of an equivalent quantity of inert material, such as charcoal or kaolin, might have produced the same result in Barbour and Lozinsky's experiments. The comparative weakness of neocinchophen as an antipyretic in rheumatic fever was indicated by the results of Hanzlik, Scott, Weidenthal and Fetterman (291)

*Heat regulation in clinical fevers* No reduction of carbon dioxide in febrile subjects with typhoid, tuberculosis and diphtheria was observed by Buss (389) after doses of from 6 to 8 grams of sodium salicylate. Frequently there was an increase in the carbon dioxide, but no diminution was observed in normal subjects. However, his method was probably not sufficiently accurate. In carefully controlled experiments, and using the Benedict respiration chamber, Barbour (411) made observations on 5 febrile, temporary febrile and convalescent subjects suffering with tuberculosis, osteomyelitis and empyema receiving 1 gram doses of acetylsalicylic acid. There was a marked antipyretic action which was not exhibited in normal subjects. In  $1\frac{1}{2}$  hours the temperature fell  $0.81^{\circ}\text{C}$  in 6 experiments on 4 subjects as against an average rise of  $0.18^{\circ}\text{C}$  on 4 control days. After the administration of the acetylsalicylic acid, the heat elimination increased 38.2 per cent, and the antipyretic effect was due mainly to this change, as with other coal-tar derivatives except possibly antipyrine. The fall in temperature was accompanied by a decrease of 3.5 per cent in heat production as compared with control days, due merely to cooling of the body. The drug caused an average decrease in pulse rate of 10 beats per minute, and some cardiac disturbance was noted in 2 out of the 5 subjects. This suggests some circulatory depression. The return to the initial temperature was brought about essentially by a reduction of heat elimination. Acetylsalicylic acid appeared to increase the respiratory quotient in these antipyretically sensitive individuals, which however was not the case in normal subjects. The sensitivity was not concerned with "stimulation" of a "depressed" heat regulating mechanism or due to lack of combustible material (dextrose).

Zimmer (412) administered cinchophen, maretin, pyrimidon and lactophenin in small doses during four to five days to moderately febrile patients with sepsis, grippe, and tuberculosis and observed the effects on the concentration of blood proteins refractometrically. The body weight generally tended to increase with the dilution of the blood, and to decrease with the increase in blood concentration. In other words retention of water occurred as the result of the administration of the antipyretics, and the mechanism of the retention was ascribed to an increase in capillary permeability. The mechanism was partly

sustained by certain effects of cinchophen on blood dilution and body weight after intravenously injected 10 per cent sodium chloride solution. However, the results of this author do not appear critical. The changes reported were small and inconstant, and the renal factor, that is, diminution in functional efficiency, was not considered. As far as blood dilution goes, the results with cinchophen and the other drugs used are in agreement with those of Barbour and his associates with salicyl. It will be recalled that Barbour attributes the blood dilution of antipyretics to the accompanying hyperglycemia, whereas Zimmer attributes it to altered capillary permeability, the latter being rejected by Barbour in his consideration of various possible mechanisms. According to Zimmer, v den Velden, in 1912, was the first to recognize a relationship between antipyresis and water content of the blood.

#### ANTIPYRETIC ACTION IN MISCELLANEOUS CLINICAL FEVERS

The use of salicyl in the form of a decoction of willow bark (most species of the large genus *Salix*) as a general febrifuge dates from ancient times. The practice continued through the medieval and up until modern times. During the Napoleonic wars willow bark was used successfully as a substitute for cinchona bark. The active constituent of willow bark is the bitter glucoside, salicin ( $C_{13}H_{18}O_7$ ), which on hydrolysis yields dextrose and saligenin, or salicyl alcohol,  $(C_6H_4(OH) \cdot CH_2OH)$ , and from which salicylic acid can be prepared. However, salicin, though effective as an antipyretic providing enough is administered, is now obsolete as a remedy because of the more easily obtained, economical and dependable synthetic salicyl compounds. For this reason it is not considered in this review, but a number of references have been appended in the bibliography for those who may be interested.

Until 1874, quinine was the antipyretic in general use for the treatment of all sorts of febrile conditions, but after that date the salicyl compounds came into use and were quite as extensively employed as quinine with equally good results. The following summary will testify to their efficiency in a variety of fevers. Their use in rheumatic fever will be considered in the next section.

Sodium salicylate was first introduced into clinical therapeutics by

C. E. Buss of Basel in 1875 (389) He demonstrated its antipyretic action in many patients with typhoid, tuberculosis, diphtheria and in four patients with rheumatic fever The dosage used ranged from 6 to 8 grams Buss' results were quickly confirmed by numerous clinicians throughout the world The occasional failures were due to inadequate dosage Wolfberg (413), for instance, found that 4 grams or less of salicylic acid was feeble and uncertain as a general antipyretic as compared with similar doses of quinine Pel (414) reported that the majority of his thirteen cases of intermittent fever were benefited by 4 to 16 gram doses According to Gehling (91) fever accompanying the puerperium with foul lochia was reduced and the lochia became less putrid when 4 to 8 daily vaginal douches of 1 1000 to 1 600 of salicylic acid were given

Good results in typhoid fever (9 cases) were reported by Nathan (415) after doses of 8 grams as the first dose and of half that much 2 hours later At the same time the pulse rate fell to normal, and the strength was somewhat increased Riegel (404) found the antifebrile effects of salicylic acid in typhoid more pronounced than with quinine, but the fever recurred and no effect on the duration of the disease was noticeable Johannsen (416) reported that about one half of his 15 cases of intermittent fever were rendered afebrile after doses of 1 5 to 3 grams given at short intervals, no effects were noted in hectic fever after 2 gram doses, there being a fall usually of  $0.1^{\circ}\text{C}$  Hiller (417) stated that he obtained favorable results in seven cases of intermittent fever after 12 to 28 grams of salicylic acid In 3 cases in which the acid was given per rectum, pain and diarrhea were observed In 23 cases of typhoid reported by Fischer (418) in which the temperature was at  $39.5^{\circ}\text{C}$  and doses of 1 to 3 grams of the salicylate or the acid were given in the evening, the temperature was reduced by morning In a study of more than 400 cases of different febrile conditions, Riess (103) found that daily doses of 5 grams of salicylic acid lowered the temperature 2, 3, 5 and 6 degrees, and often in 1 to 2 hours The more intense the fever the smaller and shorter the action In 260 cases of typhoid of which 209 were recent, and in which the temperature was at  $39^{\circ}\text{C}$ , the first dose had no effect, but later the temperature fell, and 8 to 10 doses of salicylic acid served to keep the temperature at normal The pulse rate remained uninfluenced, but



often became stronger and showed an inconstant dicrotic notch, vomiting and signs of collapse were rare. The course of typhoid fever with salicylate treatment was shortened to an average of 13.1 days in 164 cases. Antifebrile action was also demonstrated by Riess in the following acute diseases, croupous pneumonia, erysipelas, scarlet fever, rheumatic fever, and chronic phthisis. Butt (419) found 4 to 8 grams of salicylic acid to reduce the temperature in typhoid, erysipelas and rheumatic fever. Moeli (406) reported a fall of 1.5 to 3°C after comparatively large doses within from 4 to 16 hours in typhoid. This was accompanied by marked sweating. Rectal administration required larger doses, subcutaneous injection gave prompt relief. Rosenthal (420) observed no reduction of temperature in typhoid and intermittent fevers, in pneumonia a fall of about 0.8°C occurred. Hildebrandt (421) and Jahn (422) observed the fever to be lessened and the duration of the disease shortened in typhoid. Thomas (423) thought the antiperiodic action of salicylic acid was greater in malarial than in rheumatic fever, a failure being noted in only 3 out of 100 cases of intermittent fever. Raymond and Schultz (424) reported that the fever and general symptoms of scarlet fever subsided after the administration of 6 grams daily of sodium salicylate during 3 days, and complications were prevented.

Bondi (425) found that 0.25 gram of acetylsalicylic acid was antipyretic in typhoid. The antipyretic responses reported by Barbour (411) with acetylsalicylic acid in tuberculosis, osteomyelitis and empyema, and by Zimmer (412) with cinchophen in sepsis, tuberculosis and grippe, have been referred to in the preceding section.

The principal deduction from the results in this section is that the salicylates can act efficiently as antipyretics in clinical fevers in general, irrespective of their etiology, which suggests that their antipyretic action in rheumatic fever is not specific. The same holds for cinchophen.

#### ACTIONS IN RHEUMATIC FEVER

Probably the most striking clinical action of salicyl and cinchophen is the prompt and complete relief of all the symptoms of rheumatic fever. This includes the fever, the immobility of, and the pain, redness, swelling and effusions in, the joints, the general discomfort,

and the accelerated pulse and respiration. The efficiency of salicyl is so good that some have regarded it as a diagnostic and specific agent for this condition. Curiously enough cinchophen has not been so regarded, though there is no reason to believe that it acts differently from salicyl. The various aspects of the actions of these drugs in rheumatic fever may now be considered with the aim of arriving at some idea of the mechanism of their antirheumatic action.

### *General and Historical*

Although Buss (389), Riess (403) and Butt (419) demonstrated the antipyretic action of sodium salicylate in rheumatic fever, they laid no stress on the other beneficial effects that were obtained at the same time, and failed to recognize its great therapeutic value in this condition. The credit for having first recognized the full therapeutic response to be obtained with salicyl in rheumatic fever must be given to Stricker of Traube's Clinic in Berlin in 1876 (426). The observations of Stricker were confirmed during the same year by Katz (427). Stricker regarded salicylate as a radical agent and a specific cure for rheumatic fever (O. Meltzer (428)).

In Petit's contribution (429), the earlier reports on clinical cases by many clinicians are reviewed, and the beneficial effects of salicin, sodium salicylate and salicylic acid discussed. Broadbent (430) obtained beneficial results in rheumatic fever after 7.5 to 20 grains (0.5 to 1.3 grams) every hour. The pulse rate fell before the temperature, and the rheumatic pain disappeared in 4 days after the treatment was begun, the cardiac phenomena remained unchanged. Schumacher (431) stated that a complete cure in rheumatic fever may be obtained within from 12 to 48 hours, but that in a few cases there was recurrence of the disease. Steinitz (432) observed that salicylate gave a more prompt relief in rheumatic fever than other methods of treatment (injection of phenol etc.), chronic rheumatism was not benefited. G. S. (170) obtained best results in rheumatic fever. In 12 to 18 hours there was a fall of temperature, and the joint pains disappeared so that at the end of 3 to 4 days the patients could walk. S. observed no antipyretic effects in typhoid and intermittent fever. V. I. (133) observed most marked benefits in rheumatic fever after hourly doses of 0.6 gram of the sodium salicylate, the total duration

of the disease being 3 to 31 days, recurrence occurred in about 20 per cent of the cases. The drug was inactive in gonorrheal rheumatism, and other pyemic joint affections. Oettinger (434) found that recurrences and complications rarely occurred when salicylate was used. Cavañy (435) observed that pain in rheumatism was relieved in about 2 days (average). Vulpian (436) observed that from 4 to 8 grams per day in the young and adults gave relief in rheumatic fever within 48 hours. Rheumatic pleuritis, peritonitis, and encephalopathy were not influenced by salicylate. Pain in rheumatic fever, muscular rheumatism, rheumatic neuralgia, tabes dorsalis and certain cephalalgias were thought to be sometimes eased by sodium salicylate, although not generally. No influence on sensation was observed by Vulpian. In Hall's (437) cases, pain and fever in rheumatism were relieved more quickly with salicylate than without the drug. In a statistical study of results obtained with salicylates in rheumatic fever, Reihlen (438) found that 95.2 per cent of cures were effected in men, 91 per cent in women. A combination treatment of salicylic acid with salol in which the salol predominated was successfully used by Aufrecht (439) in rheumatic fever. About the only failure with salicylates in rheumatic fever was reported by Fraser (440). This occurred in patients with inflammation of the genito-urinary passages. It was explained as due to lack of tolerance of the salicyl owing to lessened elimination in renal disease, for whenever albuminuria was present, symptoms of salicylism occurred. Strictly speaking this was not a therapeutic failure of the salicyl, and, therefore, it can be said that the earlier observers unanimously agreed on the full therapeutic benefits to be obtained from the drug in rheumatic fever. This has been amply confirmed by five decades of steady usage in the treatment of this condition, and in many investigations. Even the necessity of using large doses was appreciated very early.

### *Symptomatic effects of the different salicyl compounds*

The most useful criterion of therapeutic response in rheumatic fever is the antipyretic action. With full therapeutic doses of sodium salicylate the temperature falls rapidly to the normal level, and with it the pulse and respiration are slowed and the pain disappears. The pain is lessened almost at once, but complete mobility of the joints is

usually not restored until some time after the full dosage has been administered. An early subjective recovery is frequently observed so that the patient may feel so well as to be able to move around and even leave the bed and walk on completion of the administration. In a statistical study of over 400 rheumatic patients by Hanzlik (476), complete relief of all symptoms occurred in 81.8 per cent of males and females and complete failure in only 1.6 per cent receiving sodium salicylate. In some patients the temperature becomes subnormal, in others it remains slightly febrile, leaving the patient uncomfortable. This may be due to spreading of the infection or to insufficient dosage of the drug, but sometimes a complete recovery is not obtained in spite of large doses. With the majority of patients a single course of medication, giving 1 gram doses of the drug hourly to the point of salicylism, suffices. Then the medication may be stopped, though it is the practice with many to continue the medication with small doses 2 or 3 times daily for some time afterwards as a routine. Continued medication is always indicated if the fever continues or there is an extension of joint involvement, the latter being indicated by the rise in temperature.

The lack of promptness or completeness, or both, of the response to salicyl has been taken by some to indicate the presence of some other form of arthritis or disease than rheumatic fever. However, the diagnostic significance of such a result may be questioned, for more specific remedies than salicyl, such as quinine and arsphenamine, sometimes fail to give the desired results in their own fields, that is, in malaria and syphilis. The explanation of the lack of response in occasional cases of rheumatic fever is not at hand, though it probably falls within the range of variations of biological reactions in general. Nevertheless, the therapeutic response to salicyl in the vast majority of patients with rheumatic fever is prompt and definite and probably more dependable than the therapeutic response to many other drugs in other diseases. Figure 7 illustrates typical antipyretic responses of eight patients suffering with rheumatic fever reported by Hanzlik, Scott and Gauchat (411). The results were obtained under controlled conditions and the patients received no other medication besides sodium salicylate. The majority of the patients were kept for two days without medication, then on receiving salicyl to toxic (salicylism) the temperature

fell to about the normal level at the end of 8 to 10 hours. The majority of the patients responded completely to a single full therapeutic dose, only two requiring repeated courses of salicyl medication, and in only one other patient did the temperature fall somewhat more slowly than usual. The mechanism of the antipyretic action has been discussed in the two preceding sections.

The effusion into and swelling of joints disappear some time after the pain and fever. This might be expected because absorption of the fluid is a relatively slow process. No accurate data on the time of recovery

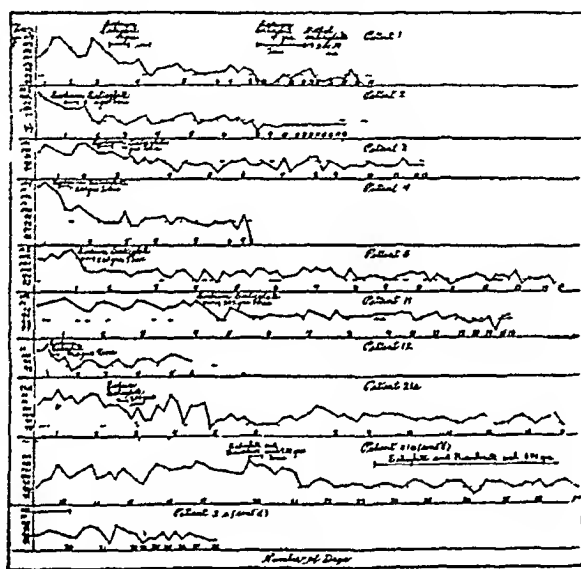


FIG 7. TYPICAL ANTIPYRETIC RESPONSES TO FULL THERAPEUTIC DOSES OF SODIUM SALICYTATE IN RHEUMATIC FEVER

are available, but, in general, recovery may be apparent or even complete at the end of 24 hours, more definitely at the end of the second to third day after a full therapeutic dose of the drug. There is considerable variability. Complete rest facilitates recovery. Moreover, the joint symptoms tend to recover spontaneously without salicyl medication as was demonstrated in the study of Hanzlik, Scott and Gauchat (441). Therefore, it may be doubted if salicyl per se facilitates the recovery of the objective symptoms in the joints independently of rest and spontaneous recovery. However, there seems to be no doubt that the relief of pain, tenderness and "soreness" when movements are

attempted is due directly to the drug. From his study of a large series of cases, Swift (442) concludes that the distressing symptoms of arthritis are easily controlled by either salicylate or neocinchophen, that the exudative features in rheumatic fever are less prominent under the full influence of salicyl than without the drug and that the disappearance of exudation and the symptoms after salicyl is the most characteristic feature of the disease. The subcutaneous nodules may appear continuously while the patient is receiving salicyl.

On the other hand, the recovery of the accelerated pulse and respiration is mainly the indirect result of defervescence of the fever. Thus is the tendency in spontaneous recovery from fevers in general. Swift (442) reports a slowing of 20 to 30 per cent in pulse rate. In the section on circulation, it was seen that full therapeutic doses of salicyl may accelerate the heart in normal individuals due probably to diminished peripheral resistance owing to the relaxation of peripheral vessels, and the respiration is simultaneously accelerated, if anything. The relative slowing of the pulse and respiratory rates in rheumatic fever is made apparent by removal of the cause (fever) of the marked increase in these functions. The changes in these functions do not have an important bearing on the general symptomatic relief in rheumatic fever.

The marked sweating of the disease is temporarily aggravated by medication with salicyl, but this only facilitates the defervescence of the fever, and therefore, recovery. The efficiency of nature's protective mechanism appears to be improved by the drug. The sweat vesicles are uninfluenced, and whether the composition of the sweat is affected or not is unknown. Unfortunately, speculations in text-books on the possible changes in the alleged marked acidity of the sweat in rheumatic fever lack a scientific basis.

Whether, or to what extent, the amelioration of the symptoms of general discomfort, that is the subjective sensation of aching, weakness and stiffness in the limbs, restlessness, etc., should be attributed directly to salicyl is debatable. There is no doubt that medication with antipyretics and analgesics, whether of the salicyl or non salicyl type, makes patients decidedly more comfortable than no medication at all. However, the experience of comfort during medication may be only the result of the relief of fever and pain.

As to duration of the disease under treatment with salicyl, this varies with the initial severity of the attack, multiple extension to joints, the individual and other factors. The mean duration in 8 patients of the series of Hanzlik, Scott and Gauchat (441) was 15 days (range 6 to 38 days), which was 9 days shorter than the duration of illness in patients on non-salicyl medication. J. L. Miller (443) found that the period of stay in hospital in treated and untreated patients did not differ. Statistics on the subject are unreliable, being subject to the individual opinion of the physician as to what constitutes a desirable period of rest. The end point is not always sharp. Swift (442) thinks that the period of rest should be as long as signs of infection persist, but the latter is not always interpreted by the same criterion, and cultures of the infective agent are precluded.

It is the general experience that treatment with salicyl alone from the beginning insures freedom from symptoms of rheumatic fever in the majority of patients. Accurate data, however, on the recurrence of symptoms are limited. In the statistical study by Hanzlik (298), about 18 per cent of the patients were incompletely or not at all relieved by the administration of sodium salicylate in full therapeutic doses, and in the large majority that was relieved, it was certain that salicyl was repeatedly administered to many patients because of recurrence of the symptoms. Two out of the 8 rheumatic patients in the series of Hanzlik, Scott and Gauchat (441) required repeated salicyl treatment for recurrence. J. L. Miller's (443) statistics showed that the salicyl treated patients relapsed more frequently than the untreated, that the freedom from pain became earlier in the treated, but that the duration of pain in the treated was no different from that in the untreated. Swift (442) found that relapses were often heralded by a declining weight so that body weight was a good index of recovery. The body weight might still fall during treatment with salicyl when other symptoms had been controlled. Swift, Miller and Boots (284) found the leukocytic curve of considerable value. That is, in the absence of evidence of concomitant non-rheumatic infection, persisting leukocytosis signified persistence of rheumatic infection, and, conversely, repeated normal counts indicated that the attack was drawing to a close, the latter being true providing the patient was not receiving salicyl medication. When the leukocytes

remained normal on discontinuance of the drug no relapse occurred and the patient recovered. When the drug was stopped and the leukocyte count increased to 4000 or more above the previous level, this showed that the infection had not stopped.

The derivatives of salicyl, namely, acetylsalicylic acid, salicyl salicylate and methyl salicylate, act qualitatively the same way as sodium salicylate in rheumatic fever. Their use in this condition has been discussed in general papers by Gordon (444) and Klaveness (445). Quantitatively, there are some differences from sodium salicylate. From a statistical study of clinical dosage by Hanzlik (298), methyl salicylate was found to be about as efficient as sodium salicylate, but acetylsalicylic acid was about  $1\frac{2}{3}$ , and salicyl salicylate, about twice, as efficient. Conversely, the effective dosage of these latter derivatives would be  $\frac{2}{3}$  and  $\frac{1}{2}$ , respectively, of that of sodium salicylate. Beneficial effects from acetylsalicylic acid in rheumatic fever were observed in connection with the study of its excretion by Hanzlik and Prescho (21). About the only advantage acetylsalicylic acid and salicyl salicylate possess is their more pleasant taste, but this does not mask the central nausea and vomiting of the "toxic" dosage. Methyl salicylate is unpleasant by mouth and its absorption is irregular and somewhat uncertain (discussed under absorption). Local application of the ester to joints is sometimes used with the idea of securing absorption and avoiding nausea, etc., but this notion is erroneous, since the ester is not sufficiently absorbed in this way to secure the systemic effects of salicyl. Any benefits from local application are due entirely to counterirritation. From 10 to 16 grams of novaspirin (anhydromethylenecitryl salicylic acid) were found by Hanzlik, Scott, Wendenthal and Fetterman (291) to be without demonstrable benefit in 3 patients with rheumatic fever. This was due to poor absorption, which amounted to a median of only 17.3 per cent of the total administered.

#### *Effects of cinchophen and derivatives*

These are precisely the same as those of salicyl just discussed and the details need not be repeated. However, some comparisons that have been made with salicyl compounds may be of interest.

It appears that Oeller (116), under Strumpell at Leipzig, in 1911,



first reported on the beneficial effects of cinchophen in rheumatic fever. A further report was made by him in 1912 (447), the best results were obtained with 3 grams given within 6 hours, when there was a rapid disappearance of redness and swelling in joints, marked sweating and prompt antipyretic action. Oeller thought cinchophen was superior to acetylsalicylic acid because the latter did not lower the temperature as promptly as, and left more cardiac side actions than, cinchophen, but it may be doubted if the dosage of acetylsalicylic acid was adequate. In the same year, Heller (290) reported that only from 25 to 50 per cent of his rheumatic patients obtained partial or temporary relief, but this lack of success appears to have been due to inadequate dosage. The subsequent reports by Bendix (448), Neukirch (449), Klemperer (450), Jokl (451), Hahn (452), and Beeck (453) on the symptomatic relief in rheumatic fever were more favorable although certain claims of superiority over salicyl by some of these authors have not been supported by later work. This statement pertains to the claim of Bendix (448) that undesirable side actions do not occur, and that of Friedberg (454) that renal irritation could be avoided with cinchophen. Neukirch (449) compared cinchophen with melubrin and acetylsalicylic acid in 8 cases of rheumatic fever and claimed that cinchophen lowered the temperature after the other 2 drugs failed. After cinchophen, the fever disappeared at the end of 48 to 60 hours, and pains in joints together with the exudation and erythema at the end of 12 to 24 hours. Out of 31 patients, 28 responded completely to cinchophen, while 2 patients, who failed to respond to cinchophen, responded to salicylate. The recurrences were no greater after cinchophen than after salicyl. Jokl (451) reported complete benefits, that is, antipyresis, analgesia, and disappearance of local heat and swelling, in 25 out of 30 rheumatic patients treated with cinchophen, and, in some, the drug acted when salicyl did not. Klemperer (450) reported successful results with cinchophen in 300 cases of rheumatic fever, and suggested that the benefits rested on a complicated antiphlogistic-analgesic action similar to that of salicyl.

In the 11 patients treated with cinchophen and neocinchophen, the therapeutic responses observed by Hanzlik, Scott, Weidenthal and Fetterman (291) were complete so that direct comparison with salicyl in the same patients was precluded, but an idea of their comparative

efficiency was obtained from the dosage of salicyl previously established. Partial symptomatic relief was obtained with doses of from 3 to 6 grams, complete relief with 10 to 13 grams of cinchophen, and with 11 to 16 grams of neocinchophen. The partial relief that was obtained by less than "toxic" doses of both cinchophen and neocinchophen indicated no special advantage over salicyl, since the same holds true of salicyl compounds and other analgesics. The dose of cinchophen was about equal to the full therapeutic dose of sodium salicylate, and, therefore, the therapeutic efficiency was about the same, while neocinchophen was less efficient, since larger doses of it were necessary to secure a complete therapeutic response. This was because of its low solubility and absorbability, which was also responsible for the small amount of gastric irritation as compared with cinchophen, the latter causing more distress than sodium salicylate. The symptoms of salicylism were about the same and renal injury somewhat less after cinchophen, and both were less pronounced after neocinchophen than after sodium salicylate in corresponding doses. The cardiac slowing produced by cinchophen was presumably due to direct circulatory depression, since it occurred in both febrile and afebrile subjects. The antipyretic action of cinchophen was more prompt and marked than with neocinchophen despite the higher doses of the latter. The diaphoresis, which occurred simultaneously, was marked with both drugs. Reduction of the fever to a subnormal level of temperature was demonstrable in the majority of patients at the end of 8 to 12 hours with the dosage of cinchophen used, but with neocinchophen it took about 24 hours for the temperature to approach the normal, though it tended to remain somewhat above the normal level. All this indicates that neocinchophen possesses a slower and less perfect antipyretic action than cinchophen and salicyl. Typical antipyretic responses of cinchophen and neocinchophen in rheumatic fever are illustrated in figures 8 and 9, respectively. Chace, Myers and Killian (293) observed a greater antirheumatic efficiency with neocinchophen than with salicyl, because the pain and swelling of joints in several patients yielded to neocinchophen after a failure to ameliorate these with salicylates, but, in general, there were small differences in the analgesic, antipyretic and uric acid elimination effects of these drugs. Barbour, Lorinsky and Clements (292) found neocinchophen fully

efficient in 12 patients with rheumatic fever, the total dosage required being from 10 to 16 grams, and 7 to 8 grams gave partial relief. The general absence of gastric symptoms and renal injury inclined them to the belief that the drug can be administered without harmful effects. Miller and Boots (294) reported that neocinchophen gave relief in some cases of rheumatic fever in which the salicylates failed, or the patients were so susceptible to the "toxic" effects of salicyl that enough could not be given. They stated that neocinchophen required

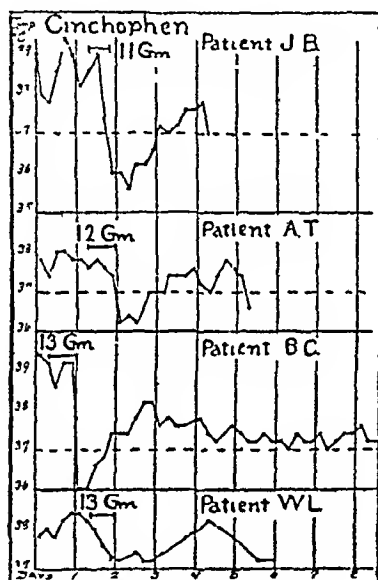


FIG 8

FIG 8 ANTIPYRETIC ACTION OF CINCHOPHEN IN RHEUMATIC FEVER

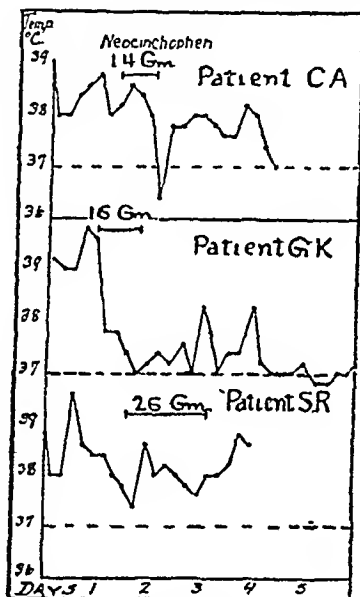
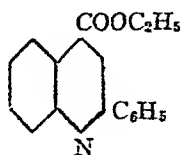


FIG 9

FIG 9 ANTIPYRETIC ACTION OF NEOCINCHOPHEN IN RHEUMATIC FEVER

large doses, but was less "toxic" and equally or more effective. As an antipyretic, however, it acted more slowly than acetylsalicylic acid, but was more lasting, this being ascribed to slower absorption, which also accounted for its being better borne. Miller and Boots (295) tried the ethyl ester of cinchophen,



in 8 patients with rheumatic fever, using total doses of from 9 to 17 grams during the first 24 hours, and after that, from 4 to 5 grams per diem during variable periods. Full therapeutic responses were obtained in 5 patients the remaining 3 showing relapses after discontinuing the drug but being relieved by acetylsalicylic acid. In the patients that were promptly benefited, the arthritis, fever, and tachycardia disappeared at the end of 24 hours. The symptoms of salicylism that were present were milder than after salicyl. As an antirheumatic remedy, this ester corresponded closely to neocinchophen, but was probably less effective than salicyl. The advantage of neocinchophen and the ethyl ester of cinchophen over salicyl, that is, the relative absence of side actions, is obviously secured at the expense of relatively poor solubility and absorbability of these drugs. The diminished efficiency, in consequence of these properties, could be corrected to some extent at least by increasing the dosage, but this means that the therapy is less economical and more inconvenient and burdensome for the patient, and, therefore, these drugs do not appear to possess the advantages over salicyl claimed for them.

#### *Cardiac lesions and the heart in rheumatic fever*

The lesions accompanying the fever may be located anywhere in the heart. However, the most common lesion is an endocarditis of the mitral valve, next in order, perhaps, is pericarditis. The observation was made by Vulpian in 1880 (436) that these lesions persist unchanged in spite of salicyl medication, and that other visceral manifestations in rheumatic fever are not arrested. In the clinical statistics of Reihlen (438), sodium salicylate was found to be neither prophylactic nor curative for cardiac complications. Cockayne (455) found the cardiac lesions in chorea also uninfluenced. From statistical studies, J. L. Miller (413) concluded that cardiac complications were not less in salicyl treated patients.

An interesting explanation of the greater frequency of endocarditis in the left than in the right auriculoventricular orifice was first suggested by Binz (456) and then by Poullson (139). It was that the carbon dioxide tension in the left heart was too low (only 2.8 per cent carbonic acid, as stated by Binz) for the liberation of free salicylic acid, which was assumed to take place in the right heart in virtue of the

higher carbon dioxide content, and to prevent the growth of organisms there Binz visualized the mechanism further as follows. He thought the carbon dioxide in the heart was not subjected to the increased pressure which was exerted in the tense fibrous tissues enveloping the joints, and that in the heart the circulation was rapid and unimpeded, while in the inflamed joints the vessels were compressed, and the blood, overcharged with carbon dioxide, flowed more slowly through them. It seemed to him that in the heart the very conditions were wanting under which salicylic acid could be liberated by carbon dioxide, and he stoutly maintained that the sodium salicylate did not circulate in the inflamed parts of the body as the salt without undergoing a change there, and without having an effect on the part. However, so far as the carbon dioxide factor in the liberation of free salicylic acid is concerned, this theory is wrong. For, in the experiments of Hanzlik (137), free salicylic acid was not demonstrable in the slightly acid (pH 6.8) cardiac (right) and arterial bloods of dogs dying of asphyxia, and it is highly improbable that the cardiac blood of rheumatic fever would contain more free carbon dioxide than that of fatal asphyxia. Finally, it was indicated in the section on distribution that a much higher degree of hydrogen ion concentration (acidity) than is compatible with life is necessary for the liberation of free salicylic acid from salicylate in the presence of serum. It was seen also that sodium salicylate is not antiseptic, the concentration of about 0.02 per cent occurring in the circulation after full therapeutic doses being far below any possible bacteriostatic action. Therefore, the explanation of the endocarditic phenomena must be sought elsewhere.

Beneficial effects of both salicyl and cinchophen on the heart are conceivable in other ways. Swift (442) interprets a favorable effect from the reduction of 20 to 30 per cent of the pulse rate due to the salicyl medication. That is, this amount of reduction in the rate reduces the number of impacts of the injured valves by a corresponding amount. The time necessary to keep the patient quiet, Swift believes, is the most important part of the treatment, and the heart naturally participates in the benefits from this period of rest. The abolition of pain, fever and insomnia is an important contributory factor. Swift suggests further that if the edema is eliminated from the valves by the antirheumatic drugs in the same manner as from periarticular tissue,

it is conceivable that the endocardium might be spared some traumatic injury. This is at least plausible. The incidence of subsequent carditis in chorea patients was found by Bertram (157) to be lower in those treated with sodium salicylate than in those treated with arsenic, sedatives or rest alone without drugs. He claimed also that salicylate was more effective in reducing carditis accompanying arthritis than in chorea. As far as heart failure in polyarthritis is concerned, Ehrstrom and Wahlberg (459) found, in an extensive statistical study, that salicyl therapy had no effect on this, nor on the infectious process, and they add that the infection would not be affected because salicyl is not a specific agent for the organism but acts symptomatically.

*Chemical structure and composition of salicyl and other agents and antirheumatic action*

It is interesting to note that it is only the ortho-hydroxy benzoic acid (salicylic acid),



which gives prompt relief in rheumatic fever. It was shown by Stockman (37) that the meta-hydroxybenzoic acid,



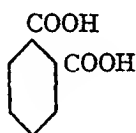
and the para hydroxy benzoic acid,



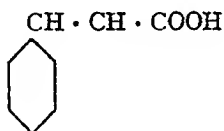
are practically inert as antiseptic and antirheumatic agents. One gram doses two hourly of these acids up to a total of about 32 grams were ineffective in rheumatic fever, and their fatal doses for rabbits

were about twice that of salicylic acid. These isomers do not give the typical iron color reaction of salicylic acid. This means that the hydroxyl (OH) group has lost its phenolic character chemically. They are, however, conjugated with sulphuric acid in the body as they are excreted as ethereal sulphates, and, therefore, behave physiologically like phenols in general (Sherwin (459)). Stockman (37) thinks that the pharmacological action of salicylic acid depends on the presence of the hydroxyl (OH) and carboxyl (COOH) groups in juxtaposition. No explanation as yet has been offered why the (OH) and (COOH) groups in other positions, as in the meta- and para-acids, do not possess the same action as the ortho acid.

Benzoic acid ( $C_6H_5 \cdot COOH$ ) was found by Stockman (37) to be effective in rheumatic fever and it caused symptoms of salicylism, but the efficiency appeared to be somewhat less than that of salicylic acid, while ortho-phthalic acid,

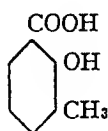


and cinnamic acid,

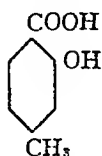


were inert.

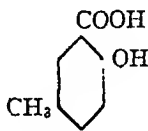
The cresotinic acids ( $C_6H_3(OH)(COOH)(CH_3)$ ) bear a close chemical resemblance to salicylic acid ( $C_6H_4(OH)(COOH)$ ), and have been tried as antirheumatic remedies. Three out of the ten isomeric cresotinic acids are known as the ortho-, meta-, and para-cresotinic acids and have structural formulae as follows:



ortho



meta



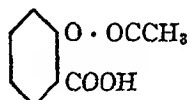
para

In all three acids, the hydroxyl (OH) group stands to the carboxyl (COOH) group in the same position as it does in salicylic acid, while the methyl (CH<sub>3</sub>) group occupies in reference to the (OH) group the ortho, meta and para positions, respectively. All three acids react chemically with iron giving a purple color, and the sodium salts all were found effective in rheumatic fever by Stockman (460). The para-cresotinate was probably somewhat less efficient than the meta- and ortho salts. The dosage necessary of all three salts was considerably higher than that of sodium salicylate. This amounted up to 40 grams for the ortho-cresotinate, and was around 32 to 36 grams of the meta- and para-cresotinate. The effects in general were almost identical with those of sodium salicylate. May (461) reported satisfactory results with sodium ortho-cresotinate in rheumatic fever, but Demme (463) decided that the sodium para-cresotinate was less efficient. Stockman (460) quotes Koranyi and Gatti as having found these compounds effective as antipyretics in typhoid, phthisis and pneumonia. In rabbits, May (461) found the lethal doses of the ortho and meta-salts to be about equal, the para-cresotinate being less poisonous. All this indicates that some modification of the physiological activity of the ortho hydroxy (OH) group in the cresotinate may be produced by changing the position of the methyl (CH<sub>3</sub>) group. However, the differences between the different cresotinate, as far as antirheumatic action is concerned, are not marked and they do not offer any advantages over the salicyl compounds.

The efficiency of salicyl compounds depends partly on the amount of salicyl which they contain or can develop in the body, and partly on other factors as yet imperfectly understood. The amount of salicyl that may be present or liberated bears on the dosage. That is, the dosage is inversely proportional to the salicyl content. Among the other factors, lipoid solubility, and the methyl, acetyl and salicyl groups play some part. This is illustrated by the relatively higher (1½) therapeutic efficiency and "toxicity" of methyl salicylate and acetylsalicylic acid than that of sodium salicylate despite the lower (86 per cent) salicyl content of acetylsalicylic acid, while that of methyl salicylate is only 5 per cent higher. The therapeutic efficiency of salicyl salicylate is about twice that of sodium salicylate, and the salicyl content, only 20 per cent higher. In the section on excretion,

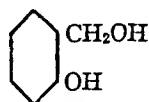


it was shown that all these compounds circulate through the body unchanged to a large extent, so that their structure is brought into intimate contact with the tissues. Originally, Dreser (11) thought that only those derivatives which would easily liberate salicyl in the tissues would be therapeutically useful, and for that reason discarded the methyl compound corresponding in structure to acetylsalicylic acid,



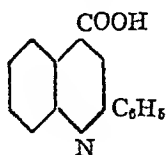
the latter answering the purpose mainly because he found it pharmacologically more active. In this he was not altogether correct because acetylsalicylic acid circulates unchanged. The mechanism of its higher efficiency is not understood, but it may be that the lipoid solubility of the acetyl, and also of the groups of the other derivatives just considered, in some way further augments the action of the salicyl group.

Salicyluric acid ( $C_6H_4 \cdot OH \cdot CO \cdot NH \cdot CH_2 \cdot COOH$ ), the conjugation product of salicylic acid and glycocholic acid, was found by Stockman (176) to be ineffective in one patient with rheumatic fever who was given 20 grams. This does not settle it, and actually the temperature was falling under salicyluric medication when sodium salicylate was administered to the patient. As far as is known, Stockman is the only one who has tried this product in rheumatic fever. Saligenin, or salicyl alcohol,

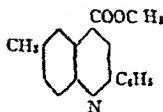


was found by Stockman (176) to be fairly efficient as an antirheumatic in total doses of about 6 grams.

That the hydroxyl group is not necessary, nor even the salicyl group, to antirheumatic efficiency is illustrated by the high efficiency of cinchophen,



and neocinchopen



which do not contain these groups. However, they are chemically related to salicyl, and their structure indicates the presence of the quinoline ring which acts as an antipyretic. Obviously important factors with all the compounds are general solubility and absorbability. The poor solubility and absorbability probably explain the relative innocuousness of neocinchopen. Novaspirin (anhydromethylenecitryl salicylic acid), for instance, is claimed to be non-toxic, etc., but its absorption amounts only to about 17 per cent (median), yet its salicyl content is high, 10 grams being the equivalent of 7.3 grams of sodium salicylate. Finally, the combined use of morphine and quinine, both of which are chemically different from all the drugs thus far mentioned, but which are nevertheless therapeutically efficient in rheumatic fever, indicates the relative unimportance of chemical composition and structure of these therapeutic drugs, and of the specificity of salicyl, in this disease. The speculations on the chemical side of this question have not led to anything definite pertaining to the mechanism of the antirheumatic action.

#### *Salicyl on streptococcal immune bodies*

This has been studied by Swift (463, 464). He determined the effects of daily doses of from 0.16 to 0.2 gram per kilo of sodium salicylate gastrically on the development of immunity in rabbits that had received intravenous injections of *Streptococcus viridans* both living and in the form of vaccines, and of washed sheep erythrocytes. As compared with the controls, the salicylized rabbits showed a depression of antibody, agglutinin and hemolysin formation and of complement fixation. The intravenous injection of antigens previously treated *in vitro* with sodium salicylate showed lower antibody curves than did the rabbits receiving untreated antigen intravenously and salicylate gastrically. The depressant action was, therefore, due partly to some direct action of salicyl on the antigen, and partly per-

haps to decreased rate of absorption of antigen in the salicylized animals This, however, is no contraindication to the administration of salicyl in the disease Swift suggests that the beneficial effects of salicyl in rheumatic fever probably can not be attributed to increased production of circulating immune bodies against the infectious agent On the other hand, the depression of the irritative properties of the etiologic agent suggests a basis for the antiphlogistic action of the drug However, a difficulty in all this is the uncertain etiology of rheumatic fever Swift's results with salicyl at least agree with the current opinion that few, if any, drugs or simple chemical substances enhance the formation of immune substances There are no studies with cinchophen

### *Salicyl in experimental arthritis*

The response of this condition to salicyl has been tested by several investigators, but unfortunately the results with both chemical and bacterial arthritis have not suggested the basis of the high efficiency of salicyl and cinchophen in the polyarthritis of rheumatic fever The selective distribution of salicyl in the joints of rabbits injected with streptococci and in those treated locally with mustard and croton oils has been discussed in the section on distribution, the results with the former were uncritical, and with the latter, negative The following are experimental results along symptomatic lines

J L Miller (443) observed that, in rabbits, the prophylactic use of salicyl had no value in preventing arthritis after intravenous injection of hemolytic streptococci Davis (465) produced arthritis in young rabbits with various streptococci and then injected from 0.2 to 0.3 gram sodium salicylate once daily for 2 weeks The salicylized rabbits died frequently before the controls and Davis concluded that the drug had no prophylactic or therapeutic effect during infection However, the method of medication used did not conform to that employed clinically That is, probably saturation of the organism with salicyl is of greater importance than gradual treatment with divided doses as employed by him The total dosage administered in his animals was large It is suggested that probably the early death of the drugged rabbits was due to nephritis caused by the salicyl superimposed on any renal injury caused by the infection Experi-

ments essentially along the same line as Davis' were carried out by Fantus, Simmonds and Moore (466) on rabbits infected with hemolytic streptococci. The dosage of sodium salicylate was 0.5 gram administered in solution and in capsules. The drug was harmless to the controls, but detrimental and fatal to the infected rabbits and the addition of sodium bicarbonate did not alter the result. Acetylsalicylic acid was more toxic than sodium salicylate, and salophen had no influence on, or was unfavorable to, the infected rabbits. Beneficial results in rabbits infected with hemolytic streptococci secured during acute tonsillitis in patients were obtained by Simmonds and Moore (467) on exposure of the rabbits to electric light continuously. All told 22 rabbits were used, and about one half the joints of the treated rabbits were involved, the lesions being more severe in the untreated controls. The temperature remained unchanged, but there was a greater gain in body weight in the treated rabbits. In another study by Simmonds and Moore (468) on rabbits infected with hemolytic streptococci, the heat factor from exposure to incandescent electric light was considered. The temperature was from 4° to 6°C above room temperature, amounting to from 33° to 35°C. Six series of rabbits were used. The controls did not die, but seemed to have more marked lesions and gave evidence of greater distress, while large numbers of the treated rabbits died though the lesions seemed to be benefited. The untreated rabbits gained more in body weight. From these results it seems that almost any treatment may be harmful to rabbits with experimental arthritis, and it may be that the hemolytic streptococci produce too severe a disease in this species.

Swift and Boots (469) compared the therapeutic efficiency of sodium salicylate in rabbits infected with the more severe hemolytic, and the less severe non hemolytic, streptococci. All 4 rabbits infected with the hemolytic streptococci, and of which 2 received sodium salicylate gastrically, died within a few days. All had purulent arthritis, but the organisms were not recovered from the joints. In a larger series of rabbits inoculated with non-hemolytic streptococci, the results were no better as to prevention of death. The rabbits received 0.16 gram per kilo of sodium salicylate daily for 5 days and then 0.08 gram for 2 days, salicyl also being given before the infection, and died sooner than the controls. Latent infections seemed to be lightened up by the salicyl

medication and the cardiac lesions were uninfluenced. Swift and Boots were of the opinion that earlier death in the salicylized rabbits was due to a summation of the bacterial action on the kidney and nephrotoxic action of the salicyl. As to the severity of the arthritis in the treated rabbits, some suggestive results were obtained. About one-half of the abnormal joints of the salicylized rabbits were found mildly inflamed, while all the controls had severe arthritis as though half the joints in the treated rabbits were improved. These are probably the first favorable results with salicyl in experimental arthritis recorded in the literature. However, previous investigators usually employed hemolytic streptococci, which, in the experience of Swift and Boots, usually cause purulent arthritis, such lesions being more nearly comparable to those of osteomyelitis, and different from the arthritis of rheumatic fever. These authors state that, since no clinical benefit is obtained with salicyl in osteomyelitis, none would be expected in rabbits with arthritis from hemolytic streptococci. However, the beneficial results in the arthritis of non-hemolytic streptococci did not agree with the mortality results, since 36 per cent of the treated rabbits died and only 8 per cent of the controls. The higher mortality signified diminished general resistance, a contrast with the apparent beneficial influence on the local infection. The increased mortality under salicyl agreed with the reduction in immune bodies shown by Swift (464). After considering various possibilities, such as a local antibacterial action of the salicyl, a reduction in the reaction of tissues to streptococcic irritation and a strong antiphlogistic action, as in mustard oil chemosis, claimed by some, Swift and Boots concluded against salicyl having exerted a beneficial action because the arthritis was neither completely inhibited nor cured as is that of rheumatic fever. They prefer to leave the question open until milder types of arthritis result from experimental inoculation and the visceral lesions resemble more closely those of patients. What anti-inflammatory action of salicyl there was occurred in rabbits inoculated with streptococci of lowest virulence.

These results suggest lines of attack in the future. Besides choosing organisms of low virulence, it would seem advisable to select a more susceptible species than rabbits for the production of arthritis. According to Hutyra and Marek (470), the acute arthritis of animals is most

common among cattle, cows being more susceptible than steers. In fact, it appears that in this species the changes in joints, endocardium and serosae, the course of infection and the causative factors are nearly identical with those of rheumatic fever in man. In dogs, horses, pigs, goats and sheep, arthritis seems to be rare. Then, the chemical and physical aspects merit consideration. In connection with the greater susceptibility of cows than steers, the possibility suggests itself that the drain on calcium in milk cows favors an increased permeability of endothelial membranes (joints, endocardium, etc.) and greater susceptibility to exudation, swelling, etc., from irritative bacteria or toxins, or both. Also, the seasonal variation in the calcium content of blood, believed to exist by some, might be a factor (when the concentration is reduced) in the seasonal appearance of arthritis in man. It seems that the metabolic aspects, at least calcium and other salt balance, should not be overlooked in determining the etiology and the exudative manifestations of rheumatic fever, even though these may be only contributory causes. Evidence is gradually accumulating to indicate that the physical chemical relationships of cells and tissues alter, if not determine, their functional state and responses to all sorts of stimuli. This is nicely illustrated by the variety of manifestations in the general group of allergic phenomena among which edema, exudations, disturbances in the circulatory (capillary) and muscular functions figure so prominently. In all these phenomena, cell surface changes, especially alterations in permeability, must be of great fundamental importance. This brings us to the antiphlogistic action of salicyl and cinchophen.

### *Antiphlogistic action*

This pertains to the relief of the inflammatory edema, effusion and pain in the joints all of which are effectively relieved by both salicyl and cinchophen. To what extent antipyresis and analgesia contribute to the relief of the local inflammatory changes in the joints of rheumatic fever is not known. However, in ophthalmia unaccompanied by fever, salicyl has been a favorite remedy for a long time. In the experimental arthritis of rabbits discussed above the antipyretic action of the drug may be a contributory factor in the relief of the joint changes, hence this experimental condition is not suitable for determining

whether the antirheumatic drugs directly ameliorate the local changes or not, i e , in the true antiphlogistic sense The question has been tested with both salicyl and cinchophen in experimental irritative edemas of the conjunctiva, lungs, and head and neck, with favorable, though uncritical, and unfavorable, results

*Mustard oil chemosis* Starkenstein and Wiechowski (230) reported that the mustard oil chemosis of rabbits could be completely prevented by the previous injection of 0.5 gram per kilo of cinchophen subcutaneously 1 hour before The preventive action was marked and constant They argued that it could not be due to a fall of body temperature, since there was only a fall of a few degrees in rabbits and dogs It was also not concerned with a peripheral anesthetic action Local application of cinchophen gave negative results The following striking analogies in the actions of cinchophen and calcium appeared to exist, both lowered body temperature, inhibited inflammation, caused emesis systemically and central paralysis and inhibited glycosuria The antiphlogistic action was not explained by analgesia, anesthesia, vasoconstriction or a local astringent action, but appeared to be concerned with some fundamental change in the tissues In a later study, Starkenstein (400) reported that non-toxic doses of cinchophen completely inhibited chemosis of mustard oil in rabbits and dionine in patients Lowering of temperature could not explain the inhibition because antipyretics in general were ineffective However, he found that antipyrine and salicylate, both of which are antipyretics, inhibited the chemosis though more slowly than cinchophen In cats, chemosis was not prevented by cinchophen and the narcosis from the drug was stronger than in rabbits, quinine and magnesium also inhibited it Believing that cinchophen acted similarly to calcium, Starkenstein (471) treated chemosis with combinations of the drug with calcium and also with santal oil and found that the preventive action of cinchophen was potentiated by calcium The action of cinchophen on purine metabolism was also favorably influenced by calcium and it was believed assisted the antiphlogistic action On the basis of these results, Starkenstein (472) extolled the use of cinchophen in the treatment of spotted fever in which the primary symptom is characterized by vascular changes, of the combination of cinchophen and calcium in inflammations with the idea of preventing the passage

of toxic agents from the circulation into the tissues, of the combination of salicyl and antipyrine in pneumonia and of cinchophen, in place of salicyl, in rheumatic fever. He (473) suggested that the so-called antiphlogistics, including cinchophen, quinine, calcium, salicyl, serum plasma, milk, methylene blue, fuchsin, iodine, collargol, physiological salt solution, etc. which he tested in chemosis, owed their action to a general protoplasmic or "omnicellular" action in the sense of non-protein therapy and involving an alteration of the entire organism toward toxic conditions. The principle of a diminished vascular permeability did not seem applicable considering the large variety of chemically and pharmacologically different agents acting similarly on chemosis, and the vascular effect did not go parallel with the therapeutic.

The generalizations of this author from the anti-chemotic action of cinchophen and other agents are too sweeping and unsupported by critical evidence. It does not follow that an antiphlogistic action in arthritis, or in systemic infections, would have the same basis as in chemosis. Moreover, critical studies of the mechanism of chemosis and certain other edemas have shown that the inhibitory actions of certain agents are concerned with circulatory depression rather than with the direct actions of drugs on the edematous tissues. It has been shown by Hirschfelder (474) for mustard chemosis and by Tainter and Hanzlik (475) for the edema of paraphenylenediamine that an adequate level of blood pressure (at least 85 mm. of mercury) is necessary in order that the edema changes may be demonstrated. A full discussion of the relationship of various functions to the development of chemosis and certain edemas will be found in a recent paper by Hanzlik (476). The majority of the agents employed by Starkenstein, including cinchophen and salicylate which were used in large doses, are capable of producing circulatory depression and this was not considered or excluded. Unless precautions are employed to maintain an adequate intravascular pressure and circulation through the affected part, inhibitory results, which are obtainable with the antichemotic and antiphlogistic agents discussed above, are apt to be misleading. The same applies to the antichemotic effects of quinine, morphine, antipyrine and salicylate in rabbits reported by Januschke (477) and frequently quoted by Starkenstein and others in support of their



claims, and also to those of cinchophen reported by Dohrn (478) All of these drugs cause general depression and all but morphine depress the circulation It is interesting to note that the mustard chemosis of cats does not respond to cinchophen, a fact reported by Starkenstein and also by Heubner and Gildemeister (479), who used 0.1 gram per kilo subcutaneously

From all this, therefore, the antichemotic actions of cinchophen and salicyl are variable and undependable, and, when obtained, they probably occur at the expense of circulatory depression, all other mechanisms that have been suggested amounting to nothing more than mere speculation Moreover, since any antichemotic action probably depends on circulatory depression and collapse, this does not conform to the occurrence of antiphlogistic action under clinical conditions Dohrn (478) claimed the discovery of an important principle in antiphlogistic action, namely, that in general the carboxylic acids, which possess antiseptic and antipyretic actions, also act as antiphlogistics though in varying degrees However, this appears to be only a coincidence and may be waved in view of the more obvious factors pointed out Some text-book writers and clinicians have attributed the benefits of antichemotic drugs, including cinchophen and salicyl, to central analgesia, and supposed that this basis accounts for the therapeutic results from these agents in rheumatism, laryngitis, bronchitis, and pleurisy, not only as to relief of pain, but also as to actual abbreviation and inhibition of the pathological process They have further recommended their use in the treatment of a variety of inflammations and infectious diseases Such unwarranted deductions and generalizations made on the basis of the seriously defective and uncritical experimental results in chemosis discussed above have led to an unjustifiable commercial exploitation of these products for all sorts of conditions, in certain of which these drugs may do more harm than good Consider, for instance, the possible injurious effects of these drugs on the kidney and heart superimposed on the injuries caused by the disease

*Mustard dermatitis* The importance of circulatory collapse and diminished blood flow through the edematous region in the antagonistic action of cinchophen is illustrated by some recent experiments of Fuerst (480) Fuerst determined the lowest effective concentration of

mustard oil producing dermatitis before and after the administration of cinchophen. The mustard oil was used in the form of small papers soaked in 30, 40, 50, 60 and 70 per cent mustard oil in olive oil and applied to the shaved skin of rabbits. Cinchophen, in very large doses, prevented the dermatitis in 66 per cent of the cases. Simultaneously these rabbits suffered a diminution in rectal and skin temperatures, and there was marked depression, but those rabbits kept warm in an electrically heated box responded with the usual dermatitis, all of which indicates that the prevention in the successful cases, was due to circulatory and general collapse. Tuerst attributed the inhibition to diminished blood flow in the skin, which, of course, would be expected in collapse. On the other hand, the administration of calcium chloride and hydrochloric acid prevented the dermatitis independently of collapse, and there was no lowering of skin and rectal temperatures. The acid base equilibrium of the blood was disturbed after both of these agents, and it appeared that a diminution in alkali reserve was responsible for the beneficial result. After cinchophen the carbon dioxide of the blood remained unchanged.

*Pulmonary edema of phosgene.* E. Lacquer and R. Magnus (481) tried cinchophen and sodium salicylate in cats and rabbits suffering with pulmonary edema from phosgene. They found that doses of from 0.1 to 0.15 gram per kilo of cinchophen dissolved in sodium or ammonium hydroxide, which were not fatal and caused either no or only a delayed and temporary fall of body temperature, caused a greater number of fatalities than occurred among the untreated controls. Sodium salicylate, in single doses of 0.15 gram per kilo or daily doses of 0.25 gram per kilo subcutaneously, had no beneficial influence on, or caused no recoveries among, the phosgenized animals. These investigators, therefore, concluded that these drugs were worthless in this irritative edema. It is true that in these experiments fatal concentrations of phosgene were employed and the pulmonary edema was severe, but under the same conditions doses of 0.167 gram of calcium chloride per kilo possessed some prophylactic value. All this emphasizes that the additive effects of cinchophen and salicyl in experimental pathological conditions are apt to be detrimental, if any thing.

*Edema of paraphenylenediamine.* In this peculiar, specific edema of the head and neck involving the cervical skin, lips, nose, orbits,

tongue, vocal cords and conjunctiva, the antiphlogistic effects of cinchophen, neocinchophen and sodium salicylate have been tested by Hanzlik and Tamter (482) with completely negative results. The blood changes in this edema consist of a marked concentration of corpuscles, hemoglobin and total solids owing to escape of plasma due to increased vascular permeability in the edema regions. The blood changes, which served as an index of permeability changes, and the appearance of the edema grossly during life and at autopsy were employed as the criteria in the study of the effects of the drugs. Sodium salicylate was administered subcutaneously in doses of from 0.15 to 0.2 gram per kilo singly and divided. Cinchophen, dissolved with the aid of sodium hydroxide, was administered gastrically in doses of from 0.1 to 0.4 gram per kilo, and neocinchophen was given as a suspension in water, using doses of from 0.25 to 0.5 gram per kilo. These doses corresponded to the full therapeutic used clinically in rheumatic fever. The drugs were given before the edema was produced, with salicylate this was from 45 minutes to 1 hour, with cinchophen from 1½ to 3 hours and with neocinchophen from 2 to 3 hours before the administration of paraphenylenediamine. At least 4 rabbits were used with each drug, and untreated control animals were observed at the same time.

FIG 10 Sodium salicylate, cinchophen and neocinchophen on the increased blood concentration in the edema of paraphenylenediamine in rabbits. The continuous lines denote changes in hemoglobin, and the broken lines, blood solids.

The results on blood changes presented in figure 10 show that salicylate, cinchophen and neocinchophen did not in any way mitigate or prevent the increase in vascular (capillary) permeability of this edema. The blood concentration was increased as much in the treated as in the control ("para") rabbits, it only decreased shortly preceding, or at time of, death, and this also occurred in the controls, a phenomenon commonly accompanying collapse or death from any cause. As far as gross edema changes were concerned these were aggravated, if anything, by the drugs, especially by cinchophen, which favored the occurrence of peritoneal

and pleural exudates. All three drugs hastened death, which is further evidence against protection, because death in the edema of paraphenylenediamine is mechanical, that is, it is of asphyxial origin due to the swelling of vocal cords, etc. Thus, it is seen that, in this irritative edema occurring without fever, the antiphlogistic effects of salicyl, cinchophen and neocinchophen were not demonstrable, a result in agreement with the negative results of Heubner and Gildemeister in chemosis and of Laequer and Magnus in pulmonary edema.

It is possible that the inflammatory changes, including the swelling, edema and exudation, in the joints of rheumatic fever are different from the experimental pathological lesions of other regions produced by chemical agents, yet there is no reason to believe that the fundamental changes in the organs and tissues are radically different. It was seen from the experiments of Swift and Boots (470) that about half the joints of arthritis in infected rabbits were somewhat benefited by the administration of sodium salicylate, yet these authors waived the conclusion that salicylate acted beneficially. Therefore, taking all the results together it appears that an antiphlogistic action due to an organotropic influence, experimentally at least, must be denied to salicyl, cinchophen and neocinchophen.

#### *Treatment of rheumatic fever with miscellaneous agents*

The fact that the symptoms of rheumatic fever have been successfully relieved, and the disease apparently cured, by a variety of agents chemically and physically different from salicyl and cinchophen is a strong argument against the specificity of these drugs. Successful treatment of a case of rheumatic fever with a vaccine, and one which would not respond to salicyl, was reported by Rosenthal and Widal (483). J. L. Miller and F. B. Iusk (484) obtained prompt recoveries in 29 out of 45 patients receiving from 4 to 75 million typhoid organisms as a vaccine. The pain, redness and swelling disappeared in from 1 to 5 days and usually within from 24 to 48 hours. The endocarditis was benefited as well as the arthritis. These patients showed no improvement after the administration of 1 to 2 grams of sodium salicylate every 4 hours. The remaining patients showed no or only partial improvement, some required reinjection of the vaccine. Comparatively speaking, the results with the vaccine were said to be

quite as good as in typhoid fever itself in which 40 per cent of cases are not benefited. The beneficial response was preceded by the usual marked reaction to vaccines (marked rise in temperature, chill, severe headache, nausea for a few hours and marked dyspnea), but there were no fatalities. Cecil (485) reported 40 per cent successes with typhoid vaccine without the aid of salicyl, but, in the remaining 60 per cent, no relief or recovery occurred until salicyl was given. Recovery from rheumatic fever may occur without medication, but Cecil believes salicyl to be the best of all the remedies and reserves foreign protein, which is a heroic remedy, for cases which fail to respond to salicyl. Scully (486) reported 40 per cent successes with one injection of foreign protein, 52 per cent with 2 injections. Apparent benefits, especially as to cardiac improvement, have been claimed by Menzer (487) with a polyvalent streptococcus vaccine prepared from tonsillitis of rheumatic fever, and by Gregory (488) in 18 children treated with a streptococcus vaccine prepared from the blood of a boy suffering with rheumatic fever. The results, however, were not exclusively due to the vaccines used, since salicyl appeared to have been used some time during the treatment. Proceeding from the notion that the arthritis of rheumatic fever is an allergic manifestation, an idea that has a certain amount of experimental support, Bauer (489) claimed successful desensitization by non-specific agents, such as caseosan, vaccines, peptone, milk, etc. In the treatment of 26 cases of arthritis with intramuscular injections of from 0.5 to 2 cc. of 10 per cent casein, repeated after 4 or 5 days, Roch and Katzenellenbogen (490) obtained most satisfactory therapeutic results in rheumatic fever. They advise the casein as a supplementary measure. According to Kaess (491) any kind of protein in optimal dosage, subcutaneously or intravenously, gives beneficial results in all kinds of arthritis, a preliminary sensitization frequently giving a better result.

The following non-protein colloids are reported to give full therapeutic benefits in rheumatic fever, and frequently when patients are refractory to salicyl medication. The use of colloidal sulphur, 1 to 2 cc. daily for 2 days intravenously, is reported by Massalongo (492) and Viola (493). It caused rapid amelioration of all symptoms and marked sweating. Giroux (494) affirms the efficiency of this agent, but states that it produces violent reactions, and that colloidal gold

intravenously in a dose of 0.25 cc, then 0.5 to 1 cc, is also efficient. Blumenthal (495) advocates colloidal silver intravenously in patients refractory to salicyl, and Martone (496), from 1 to 5 mgm daily doses of mercuric chloride intravenously.

Widal (497) quotes the successful use of antipyrine 3 to 4 grams daily, and rarely more than 8 grams, by G. Sée, and by Chauffard who used atropine with it conjointly, of sodium benzoate by Senator, of salpyrine and phenacetine by Masius, of asprol by Dujardin-Beaumetz, and of phenocoll.

Lampronti (498) claims to obtain best results by injecting 8 cc of 3 per cent antipyrine directly into a joint, 12 cc being distributed among other joints so that not over 20 cc are given during 24 hours. The solution consists of 1.5 grams antipyrine in 46 grams of distilled water, and after sterilization by heat, 4 grams of 0.1 per cent epinephrine solution are added. He claims that the pain ceases almost at once, the temperature falls in a few hours, absorption of the edema follows quickly and the local reaction is slight. Melubrin, which is a pyrazolone derivative closely resembling antipyrine, has been used successfully in 1 gram doses 3 to 4 times daily up to 10 grams in rheumatic fever by Hoppe (499), who claims the effects resemble closely those of salicyl. It acts as a general antipyretic.

Whether the use of the different agents that have been mentioned is justified or not, especially the vaccines, proteins and colloids intravenously, the results that have been reported nevertheless indicate that symptomatic benefits, and even cures, in rheumatic fever are obtainable with a variety of unrelated agents. In fact, the symptoms constitute the only criterion by which the efficacy of antirheumatic remedies can be judged: salicyl and cinchophen included. Accordingly, therefore, the so called specific remedy (salicyl) falls into the same category as the non specific (diverse agents), which merely indicates that the beneficial result is not peculiar to, or specific for, salicyl. As to the comparative therapeutic efficiency of salicyl and the miscellaneous agents that is another matter, and there are marked differences of opinion on this point.

#### *Non-specificity of salicyl*

From the results that have been discussed thus far, it is apparent that the therapeutic response with salicyl and cinchophen in rheuma-

quite as good as in typhoid fever itself in which 40 per cent of cases are not benefited. The beneficial response was preceded by the usual marked reaction to vaccines (marked rise in temperature, chill, severe headache, nausea for a few hours and marked dyspnea), but there were no fatalities. Cecil (485) reported 40 per cent successes with typhoid vaccine without the aid of salicyl, but, in the remaining 60 per cent, no relief or recovery occurred until salicyl was given. Recovery from rheumatic fever may occur without medication, but Cecil believes salicyl to be the best of all the remedies and reserves foreign protein, which is a heroic remedy, for cases which fail to respond to salicyl. Scully (486) reported 40 per cent successes with one injection of foreign protein, 52 per cent with 2 injections. Apparent benefits, especially as to cardiac improvement, have been claimed by Menzer (487) with a polyvalent streptococcus vaccine prepared from tonsillitis of rheumatic fever, and by Gregory (488) in 18 children treated with a streptococcus vaccine prepared from the blood of a boy suffering with rheumatic fever. The results, however, were not exclusively due to the vaccines used, since salicyl appeared to have been used some time during the treatment. Proceeding from the notion that the arthritis of rheumatic fever is an allergic manifestation, an idea that has a certain amount of experimental support, Bauer (489) claimed successful desensitization by non-specific agents, such as caseosan, vaccines, peptone, milk, etc. In the treatment of 26 cases of arthritis with intramuscular injections of from 0.5 to 2 cc of 10 per cent casein, repeated after 4 or 5 days, Roch and Katzenellenbogen (490) obtained most satisfactory therapeutic results in rheumatic fever. They advise the casein as a supplementary measure. According to Kaess (491) any kind of protein in optimal dosage, subcutaneously or intravenously, gives beneficial results in all kinds of arthritis, a preliminary sensitization frequently giving a better result.

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### *Nor specificity of salicyl*

From the results that have been discussed thus far, it is apparent that the therapeutic responses with salicyl and cinchophen in rheuma-



tic fever are indistinguishable, and, it may be added, also with certain of the miscellaneous agents just discussed. Yet, it is the salicyl group that is alleged to be the specific remedy in this disease. Why cinchophen is not generally included is not clear. The idea of specificity has no better basis than an old clinical impression, unsupported by objective evidence of any kind, and which seems to have been first expressed by Stricker in 1876, who first recognized the merits of salicyl in rheumatic fever. G. Sée (150), who popularized the drug in France in 1877, had the same idea. This idea has been perpetuated down to the present day and is the conception of salicyl action presented in most text books of pharmacology and therapeutics. However, from time to time doubts of its validity have been expressed, and during the past 10 years or so the idea of specificity among investigators and students of the subject has been abandoned. This position has been taken because of the efficacy of other kinds of therapy in rheumatic fever without the aid of salicyl, and of results from direct comparison of salicyl and non-salicyl medications in the same and different patients.

It is interesting to note that Ehrlich (500) accepted the specificity of salicylates in rheumatic fever on the antiseptic basis, although he realized that the etiology of the disease was unknown. The conceptions which he formulated for salicyl, and which were part and parcel of the principles which he followed in his search for specific chemotherapeutic agents, were about as follows. He stated that there were only 4 agents which exerted a specific action in infectious diseases and these were quinine in malaria, mercury in syphilis, salicylic acid in rheumatic fever, and trypan red and arsenic in trypanosomiasis. Out of the 3 principles in chemotherapy that had to be met by drugs, according to him, namely, (a) a strong inhibitory or bactericidal action in vitro, (b) relative harmlessness to the organism or host, and (c) antiseptic action in the organism, salicylate complied only with the second. From this it is difficult to follow the logic of the postulated specificity of salicyl, but on the contrary would seem an argument against it. What held then with respect to the antiseptic actions of salicyl in vitro and in vivo, holds with equal force now, as indeed has been conclusively demonstrated by the results of the researches cited. This is not the place to consider the etiology of

rheumatic fever though it is obviously a paramount factor in any consideration of the specificity of anti-rheumatic drugs. Here it must suffice to cite only the results bearing on the question with respect to salicyl and cinchophen. In order to be convinced of the fact that the etiology of rheumatic fever remains undetermined one needs only to consult the works of the following authors: Vidal (497), Rolly (501), Topley and Weir (502), Riesman (503), Boots and Swift (504), Swift (505, 442), Turnbull (506), Vaughn (507), Giroux (194), W. G. MacCallum (508), and Swift, Andrews and Derrick (509). All this, therefore, completely eliminates the etiotropic action of salicyl from the consideration of its specificity, and leaves only the symptomatic relief.

In 1908, Stockman (510) suggested that too much stress must not be laid on the specificity of salicyl because it gives relief, though partial, in conditions other than rheumatic fever, relapses occur even while the patient is taking the drug, and other drugs are nearly as efficient as salicyl. R. Miller (511) objected strongly to the view that salicylates are specific for rheumatic fever, and cited partial and complete relief in other conditions. He also compared the excretion in urine of normal and diseased individuals and found the rate to be about the same. In the excretory study of Hanzlik, Scott and Thoburn (162), no difference in the avidity of rheumatic tissues from the non-rheumatic was demonstrable because the duration of excretion was the same, although quantitatively the excretion in rheumatic fever was about 20 per cent less owing to increased destruction of the drug. In the statistical study of clinical cases by Hanzlik (298), it was seen that sodium salicylate brought about the greatest number of complete responses in rheumatic fever and partial responses in other conditions, but this might have been due to the greater preponderance of rheumatic fever patients treated. A statistical study could not obviously settle the question of specificity, and at best might indicate only some differences as to therapeutic efficiency of the drug. From a study of 212 cases, Zidek (512) concluded that sodium salicylate was not specific because neither salicyl nor anything else would prevent relapses, and the involvement of new joints or of the heart, salicyl reduced the pain and enabled freer movement of the joints while the temperature declined under it, but the same results were obtained

occasionally by physiotherapy Frenkel (513) believes that the specific results with salicyl in rheumatic fever are based on a misapprehension, the disease is of a remittent or intermittent character, the natural intermission coming on after taking the drug and the attenuation of symptoms is wrongly ascribed to the drug when in fact the drug is not responsible for it This is probably overstated, but he claims to have observed, in his clinic, patients going through parallel phases of exacerbation and remission whether salicyl was given or not Swift, Miller and Boots (284) consider rheumatic fever a self-limited disease From his extensive studies of rheumatic fever and comparisons of the therapeutic efficiency of salicyl, cinchophen and neocinchophen under controlled conditions, Swift (348, 442) is convinced that the drugs that have been considered as specifics are probably only antisymptomatic in their action, an important feature against the specificity being the frequent discovery of persisting infection However, he believes that the drugs are still valuable for controlling the distressing febrile, arthritic and cardiac symptoms Ehrstrom and Wahlberg (458) deny any effect of salicyl on the infectious process and conclude that salicyl is only a symptomatic remedy, and Libarona (514) states that the drug does not differentiate rheumatic fever from other arthritic conditions

A direct test of the question of specificity of salicyl in rheumatic fever was made by Hanzlik, Scott and Gauchat (441) The method consisted of the comparison of salicyl and non-salicyl medications in patients who were in bed and receiving no other medication The patients were first treated with non-salicyl medication, and if no relief was obtained within a reasonable period of time, as indicated by the progress of the condition, sodium salicylate up to salicylism in the usual way was administered That is, the antipyretic and analgesic properties of salicylate were imitated by combinations of other drugs such as morphine or papaverine, and quinine or acetphenetidine, which are chemically different from salicyl, but possess similar antipyretic and analgesic qualities In this way, the symptoms could be readily combated, and if complete relief ensued without further medication, no specificity for salicyl, either etiologic or symptomatic, could be claimed The criterion of complete relief was the prompt and permanent relief of all subjective and objective symptoms

of the disease, partial relief was the partial or imperfect relief of the symptoms and the persistence of symptoms unabated was called "no relief." Rather large doses of the combined opiates and antipyretics were used, as this was believed to be correct in principle, for it appeared that the prompt and full therapeutic response to salicyl was due to the marked effects of the massive doses employed. Figure 11 illustrates the comparative antipyretic efficiency of the combined opiate-antipyretic medication and salicyl in the 9 rheumatic fever patients that were observed. This figure may be compared with

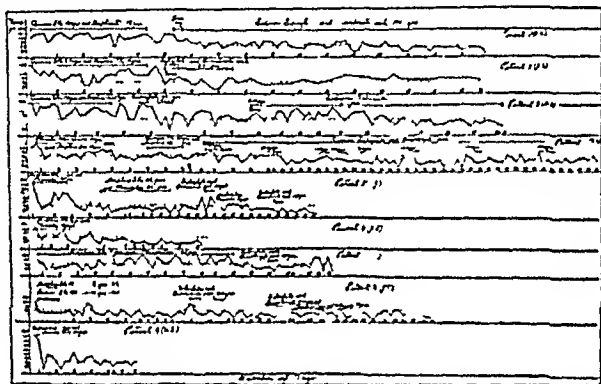


FIG. 11 COMPARATIVE ANTHYRETIC EFFICIENCY OF NON SALICYL (OPIATE ANTHYRETIC COMBINATIONS) AND SALICYL MEDICATION IN RHEUMATIC FEVER

figure 7, illustrating the results with 8 patients receiving salicyl alone, and which served as a further control for the opiate antipyretic group.

In brief, prompt though partial relief was obtained in the majority of patients receiving the non salicyl medication. This was true for both early and late symptoms. In some patients, the symptoms persisted despite salicyl medication, and in at least 4 out of the 17 patients (2 receiving the non salicyl and 2 salicyl medication) there was a recurrence shortly after treatment with salicyl. In those patients in whom the symptoms persisted, although considerably moderated, after treatment with the non salicyl antipyretics and

analgesics, salicyl appeared to give more permanent relief. On the other hand, in 2 of the patients the fever persisted in spite of the salicyl medication. In some of the patients, the persisting antipyretic action during salicyl medication, although other symptoms of the disease were present, may have been due to the retention or delayed action of the non-salicyl antipyretic. Four out of the 9 patients receiving non-salicyl medication were not relieved of any of the symptoms until salicyl was administered. Eliminating the elements of time, rest, and natural recovery, it appeared that the relief of later symptoms was brought about more effectively and permanently by salicyl, than by non-salicyl, drugs. Although the number of patients was not large, the results, as far as acute symptoms of rheumatic fever are concerned, showed definitely that these can be promptly and effectively relieved by combinations of drugs whose pharmacological actions are similar to, but which are chemically different from, salicyl. It is also possible to obtain permanent relief with combinations of non-salicyl antipyretics and analgesics. Since these results agree with those of several other investigations in which the problem has been approached from other angles, as indicated above, there is therefore a large amount of collective evidence, entirely unopposed, against the idea that the salicylates are specific in rheumatic fever.

*Mechanism of the antirheumatic action of salicyl and cinchophen*

After all that has been said throughout the text thus far, it remains only to recapitulate briefly the important evidence bearing on, and conclude as to the probable nature of, the mechanism of therapeutic action of salicyl and cinchophen in rheumatic fever. Special attention to the elucidation of the mechanism of salicyl action has been paid only in more recent times, credit, however, being due to the modest efforts of Binz (52, 457) in 1876. The long period of sterility in this direction is to be attributed to the blind patronage of the fallacious postulate of specificity. All the evidence is against the antiseptic action of salicyl under conditions of the body. There is no etiotropic action for the simple reason that the etiological factor is not understood, and for this reason a satisfactory experimental arthritis has not yet been produced to test this proposition directly, and from the fact that antiseptics against an organism, whether bacterium or

parasite, is improbable. An antiphlogistic action through a strictly local organotropic influence is experimentally untenable. The only possibility that exists along this line is an altered (increased) permeability of the vessels with changes in local blood flow, or of articular tissues, or both, which might facilitate the absorption of fluid, toxins, products of inflammation, etc., from the joints. This is not a mere fancy, for an increase in permeability of the kidney to uric acid has been demonstrated with both salicyl and cinchophen, and of living loops of intestine to salts with salicyl, but as far as the joints are concerned it amounts to no more than speculation. Measurements of blood flow through the joints do not exist. Against the idea is clinical evidence of the prompt recovery of the joints without medication. That leaves antipyresis and analgesia, which are definite actions of both salicyl and cinchophen. Both actions occur in a variety of conditions other than rheumatic fever, as will be indicated in the following section. Antipyresis has been demonstrated experimentally and its cause is well understood, though not so the analgesia. Nevertheless, the antipyretic and analgesic actions are general and unquestionable. Hence, it appears that the relief of rheumatic fever by salicyl and cinchophen is mediated through the antipyresis and analgesia produced by these agents, which act rather efficiently, permitting comfort and rest while the joint symptoms disappear spontaneously and gradually. These drugs are only symptomatic remedies, which can be safely administered in very large doses, and represent a fortunate combination of both antipyretic and analgesic qualities which make them more suitable, convenient and desirable than the employment of 2 or more drugs possessing the same actions individually. Their high efficiency and desirability as symptomatic remedies in rheumatic fever may be regarded as outweighing any of the seriousness from the temporary disturbances of renal function, and other side actions.

#### ACTIONS IN MISCELLANEOUS CLINICAL CONDITIONS

In the following summaries it will be seen that salicyl and cinchophen enjoy an extensive usage in a variety of disease conditions etiologically different. This usage depends on symptomatic relief that is, of pain, fever or inflammatory swelling. It is probably the

analgesics, salicyl appeared to give more permanent relief. On the other hand, in 2 of the patients the fever persisted in spite of the salicyl medication. In some of the patients, the persisting antipyretic action during salicyl medication, although other symptoms of the disease were present, may have been due to the retention or delayed action of the non-salicyl antipyretic. Four out of the 9 patients receiving non-salicyl medication were not relieved of any of the symptoms until salicyl was administered. Eliminating the elements of time, rest, and natural recovery, it appeared that the relief of later symptoms was brought about more effectively and permanently by salicyl, than by non-salicyl, drugs. Although the number of patients was not large, the results, as far as acute symptoms of rheumatic fever are concerned, showed definitely that these can be promptly and effectively relieved by combinations of drugs whose pharmacological actions are similar to, but which are chemically different from, salicyl. It is also possible to obtain permanent relief with combinations of non-salicyl antipyretics and analgesics. Since these results agree with those of several other investigations in which the problem has been approached from other angles, as indicated above, there is therefore a large amount of collective evidence, entirely unopposed, against the idea that the salicylates are specific in rheumatic fever.

*Mechanism of the antirheumatic action of salicyl and cinchophen*

After all that has been said throughout the text thus far, it remains only to recapitulate briefly the important evidence bearing on, and conclude as to the probable nature of, the mechanism of therapeutic action of salicyl and cinchophen in rheumatic fever. Special attention to the elucidation of the mechanism of salicyl action has been paid only in more recent times, credit, however, being due to the modest efforts of Binz (52, 457) in 1876. The long period of sterility in this direction is to be attributed to the blind patronage of the fallacious postulate of specificity. All the evidence is against the antiseptic action of salicyl under conditions of the body. There is no etiotropic action for the simple reason that the etiological factor is not understood, and for this reason a satisfactory experimental arthritis has not yet been produced to test this proposition directly, and from the fact that antiseptics against an organism, whether bacterium or

parasite, is improbable. An antiphlogistic action through a strictly local organotropic influence is experimentally untenable. The only possibility that exists along this line is an altered (increased) permeability of the vessels with changes in local blood flow, or of articular tissues, or both, which might facilitate the absorption of fluid, toxins, products of inflammation, etc., from the joints. This is not a mere fancy, for an increase in permeability of the kidney to uric acid has been demonstrated with both salicyl and cinchophen, and of living loops of intestine to salts with salicyl, but as far as the joints are concerned it amounts to no more than speculation. Measurements of blood flow through the joints do not exist. Against the idea is clinical evidence of the prompt recovery of the joints without medication. That leaves antipyresis and analgesia, which are definite actions of both salicyl and cinchophen. Both actions occur in a variety of conditions other than rheumatic fever, as will be indicated in the following section. Antipyresis has been demonstrated experimentally and its cause is well understood, though not so the analgesia. Nevertheless, the antipyretic and analgesic actions are general and unquestionable. Hence, it appears that the relief of rheumatic fever by salicyl and cinchophen is mediated through the antipyresis and analgesia produced by these agents, which act rather efficiently, permitting comfort and rest while the joint symptoms disappear spontaneously and gradually. These drugs are only symptomatic remedies, which can be safely administered in very large doses, and represent a fortunate combination of both antipyretic and analgesic qualities which make them more suitable, convenient and desirable than the employment of 2 or more drugs possessing the same actions individually. Their high efficiency and desirability as symptomatic remedies in rheumatic fever may be regarded as outweighing any of the seriousness from the temporary disturbances of renal function, and other side actions.

#### ACTIONS IN MISCELLANEOUS CLINICAL CONDITIONS

In the following summaries it will be seen that salicyl and cinchophen enjoy an extensive usage in a variety of disease conditions etiologically different. This usage depends on symptomatic relief, that is, of pain, fever or inflammatory swelling. It is probably the



analgesia that is most commonly aimed at. All this helps to confirm the notion that they are symptomatic and not specific remedies, although in certain of the miscellaneous conditions they appear to be less efficient than in rheumatic fever. However, many factors enter into their efficiency, of which dosage is obviously one of the most important. Also, most of the miscellaneous conditions are chronic disorders in which a temporary or partial therapeutic response is the rule whatever the therapy. Therefore, only a moderate degree of therapeutic efficiency from these drugs would be expected.

*Arthritis deformans.* C. F. Kunze (515) stated that the pain was lessened by sodium salicylate, but G. Sée (150) saw no improvement. Mark (516) could reduce the hypercalcemia of this condition on a calcium-free diet though not to normal, and acid, alkali and sodium salicylate changed the ratio of calcium excretion in urine and feces, but did not alter the slight negative balance on a calcium-poor diet.

*Chorea.* Successful treatment of this condition has been reported by Fraser (517), but usage of salicyl in this condition varies with opinions of its etiological relationship to rheumatic fever.

*Chronic gastro-enteritis.* Justi (386) advised 0.5 to 0.6 gram for adults as beneficial in this condition. He regarded the use of sodium salicylate as having a favorable influence on digestion. Beneficial effects were obtained by Wagner (518) in treating gastric fermentation, stomatitis, intestinal decomposition and other similar conditions with salicylic acid.

*Coryza.* Sick (519) recommended acetylsalicylic acid as a prophylactic in one to two doses of 1 gram each to be taken at the first indication of "cold in the head," or "tickling in the throat." For cough, it was recommended by Ebstein (520). It is extensively used, in fact has become a household remedy, in colds, headaches, etc., in tablets or capsules of 0.3 gram, acting more efficiently as an antipyretic and analgesic here than sodium salicylate.

According to Barbour, Lozinsky and Clements (292), neocinchophen gives effects in colds similar to those of acetylsalicylic acid, but the action is slower and somewhat larger doses are indicated, in tonsillitis 1 to 2 grams.

*Diabetes.* Ebstein and Muller (521) reported a diminution in the volume of urine and a marked reduction of sugar after doses of 15

grams per day of sodium salicylate v Brnken (522) reported a disappearance of glycosuria after four doses of 0.5 gram each of salicylic acid followed by 8 to 9 grams of sodium salicylate G Muller-Warneke (523) stated that 9 to 10 grams given daily in three to four single doses caused the glycosuria to disappear so long as the agent was used No side actions were noticeable, except albuminuria, which disappeared when the agent was stopped In the majority of patients studied by Furbringer (524), no beneficial effects on sugar and urine excretion were observed No beneficial results beyond a diminution in sugar excretion were observed by Kaufmann (525) in the majority of his patients with diabetic coma The production of the diabetic type of acidosis in animals after salicyl was pointed out in the section on blood

*Encephalitis* Carnot and Blamontier (526) reported prompt benefits in a grave case of epidemic encephalitis of the choreic type after intravenous injection of 4.5 grams sodium salicylate daily up to a total of 22 grams, and in a boy with lethargic encephalitis who received 50 grams in 8 days The same is claimed by Denechau and Barbary (527) in epidemic encephalitis of a woman who received 0.5 gram sodium salicylate in 4.7 per cent dextrose intravenously and 1 gram intramuscularly during 22 days

*Erythema nodosum* H Ehrlich (528) claimed benefits in a case from "leukotropin" 10 cc intravenously, and Richartz (529) from cinchophen in 5 cases

B Mendel (279) reported benefits from 1 gram "leukotropin" in 7 cases of eczema

*Gout* Kunze (515) stated that the pain in gout was lessened by salicylate Combined with colchicin, Cullen (530) also found salicylate to be very beneficial in removing pain in gout

Cinchophen, however, has had a greater popularity than salicyl in gout The principal basis of its use here is analgesia Its use in the treatment of this condition appears to have been introduced by Weintraud in 1911 (221), although in 1908 Nikolauer and Dohrn (28) used it in their studies of uric acid excretion in gout on the fancied etiological connection of this metabolite with the condition Weintraud (236) used doses of 10 grams, the drug also lowered the temperature in typhoid He reviewed the literature of the time Better

results in acute than in chronic gout were reported by Deutsch (531) who treated 25 cases, the drug had to be given with sodium bicarbonate owing to undesirable side actions Georgiewsky (330) reported benefits with daily doses of 0.5 gram for 10 days, and Zuelzer (532) claimed the drug's action was so good as to be diagnostic Meidner (533) reviewed the benefits of cinchophen and salicyl in gout and other conditions Retzlaff (223) claimed best results in gout with 2 to 3 grams daily for 4 to 5 days Klemperer (450) referred to the use of cinchophen and neocinchophen, claiming that the only objective effect understood was the increased uric acid excretion, however, he used cinchophen extensively in rheumatic fever as an antiphlogistic and analgesic Friedberg (454) reported 11 cases in which 0.5 gram three times daily stopped the pain, a total dosage of from 8 to 10 grams being used

*Influenza* Acetylsalicylic acid, in small doses of about 0.3 gram, is commonly employed here as an antipyretic and analgesic as in "colds" Neilson (534) claims success with sodium salicylate intravenously in relieving the pain, restlessness and toxemia, but advises against its use in pneumonia Ammonium salicylate is reported to be "curative" and preventive (535), however without evidence to support this, and probably it acts like any salicyl compound H Ehrlich (528) claims benefits in this condition with "leukotropin"

*Muscular rheumatism* This was seen to be benefited by G Sée (150), Schuster (536) and Demieville (537), who injected from 4 to 7 cc first, and later 10 to 12 cc, of 2 per cent sodium salicylate into the painful areas of large muscles, also a case of rheumatic tetanus by Wunderlich (538).

*Neuralgia and sciatica* Acetylsalicylic acid, in small doses, is commonly employed in neuralgia Marked relief was reported by L Hoffmann (539) after hourly or two-hourly doses of 0.5 gram each of sodium salicylate for ten to twenty doses Salophen was reported by Lutze (540) as a good antineuralgic Success in facial paralysis with salicyl ion medication by electrophoresis is claimed by Fiorini (541). In sciatica, Demieville (537) reported good results after intramuscular injection of hot 2 per cent sodium salicylate solution Good results with cinchophen have been claimed by Hirschberg (542)

*Pleurisy with effusion* Koster (543) recommended 1.5 to 3 grams

of sodium salicylate four times daily as an aid in the absorption of the exudate. Beneficial effects were observed in seventeen out of twenty-seven cases. However, according to Leonhardi-Aster (544) the inflammatory process in the pleura remains unchanged. Leonhardi-Aster also observed such side actions as hemorrhagic pleuritis and hematuria in patients taking salicyl. The use of salicyl in certain serous inflammations is also discussed by E. Smith (545).

*Pneumonia* Beneficial therapeutic results were obtained with salicylic acid by Sebring (546), the convalescence was shortened, fever fell gradually, the pulse remained full and not overrapid and no cardiac complications were observed. Benefit with "leukotropin" intravenously has been claimed by H. Ehrlich (528).

*Psoriasis* Repeated intravenous injections of sodium salicylate (12 cc. of 20 per cent) were employed by J. F. Smith (547) in 57 cases, symptoms disappeared in 16 per cent, and partial improvement occurred in 32 per cent. On the other hand, Maloney (548), using the same method and drug, obtained only slight benefits in 20 cases, and suggested that salicylic acid externally would be as efficient as the sodium salt intravenously.

*Pulmonary gangrene* Beneficial results were reported by Berthold (549).

*Scarlet fever* Ramond and Schultz (424) claim good results with 6 grams and upwards of sodium salicylate daily until fever and general symptoms have subsided which usually occurs in 3 days. The medication is resumed on the fifteenth day to prevent complications. Under salicyl the complications are milder and mortality low.

*Subacute and chronic rheumatism* No beneficial results with sodium salicylate were observed by G. See (150). Roeh (550) asserted that acetylsalicylic acid lowers the temperature here about as well as in other febrile conditions. After prolonged medication beneficial results were observed by Schuster (536). After application of salicylic acid (as ointment) to the skin, no beneficial effects were obtained by Bourget (64). In podagra, Kunze (515) reported that swelling of the joints is not influenced by the administration of sodium salicylate. In war wounds of joints, Impallomeni (551) used successfully subcutaneous and intramuscular injections of 1 gram of sodium salicylate in 100 cc. containing 0.01 gram of stovaine.

Beneficial effects from cinchophen in chronic arthritis are denied by Oeller (447) and Richartz (529). Partial benefit is claimed by Brahn (552) with "leukotropin" (a mixture of hexamethyleneamine and cinchophen) 8 to 10 cc intravenously, also by H. Ehrlich (528) who used 10 cc.

*Sympathetic ophthalmia* H. Gifford (553) introduced the use of salicyl in this condition. He observed marked beneficial effects and recoveries with sodium salicylate, acetylsalicylic acid and other salicyl compounds. The usual dosage was 30 grains (about 2 grams) and the mechanism of action suggested was depletion of inflamed tissues by the dilation of capillaries. Others, cited by Whitham (110), as having had experiences similar to those of Gifford are, Welton (554), Bane (555), Campbell (556), deSchweinitz (557), C. Wood (558), Webster (559), Baker (560), Heuse (561), Lindahl (562), Widmark (563) and Lees (268). Moulton (564) advises 1 grain (0.06 gram) sodium salicylate for each pound of body weight to be taken in 10 to 14 hours in panophthalmitis from injury, the salicyl prevents blindness. According to Campbell (565), salicyl is of definite value in certain inflammations of the uveal tract especially in sympathetic ophthalmia. Besides lessening pain and promoting rest and sleep, he thinks the inflammatory process is directly benefited. Very large doses give the best results. Acetylsalicylic acid gives more prompt analgesia, and is also useful after operations on the eye, doses of about 10 grains (0.7 gram) before retiring assure rest. The studies of S. R. Gifford (117) on the distribution of salicyl in experimentally infected and normal eyes were discussed in the section on distribution, there were no significant differences. The antiphlogistic action in ophthalmitis presumably, therefore, does not depend on a selectivity of the salicyl, agreeing in this respect with the effects in other edemas.

*Varicose veins* Benefits are claimed by Dunbar (566) and Grzywa (567) in over 30 cases. The veins are injected with 1 cc of 20 per cent sodium salicylate, and, if no local reaction occurs, up to 40 per cent is injected. The total dose of the drug should not exceed 3 grams. This treatment is claimed to be no worse or better than the surgical, but tends to improve the circulation in the legs. It will be recalled that salicyl softens tissues and dilates the peripheral vessels, but the possibility of sloughing should be kept in mind.

## TOXICITY

The symptoms of poisoning by salicyl and cinchophen are similar and resemble those of cinchonism, or salicylism. On account of its close relationship to phenol, salicyl was early suspected of toxicity, but it is the derivatives that have been more responsible for the marked and peculiar side actions and fatalities than sodium salicylate. The literature contains no report of fatalities from cinchophen and its derivatives. The fatal dose varies with the compound or derivative and with the species. For convenience the fatal and toxic doses of the more important preparations in different species determined or reported by various authors and the methods of administration used, etc., have been summarized in table 2.

*Fatal dose*

The fatal dose of the salicyl group in different animals has been determined by Laborde (568), Walter (265), Blanchier (97), Oltramare (356), Chanoz and Doyon (569), Houghton (77), Block (160), Waddell (296), Dreser (40) and Barbour and Lozinsky (299). From the summary in table 2, it is seen that there is some variation in the fatal doses of any given compound or derivative depending partly on the method of administration and partly on other factors. Consideration of the details will be omitted. In general, it may be said that the fatal dose of sodium salicylate is from 1 to 1.5 grams per kilo for all species irrespective of the method of administration, and that the fatal doses of methyl salicylate, acetylsalicylic acid and probably also salicyl salicylate (salysal) are less, i.e., anywhere from 50 to 80 per cent less. However, the data on the fatal doses of the derivatives are incomplete, but the toxic doses in human subjects, which have been ascertained on a statistical basis by Hanzlik (298), agree with this tendency. The fatal dose of sodium salicylate in man is not definitely known, but may be somewhat less than, or about, 1 gram per kilo. Allaire (570) reported a fatality from 30 grams, and Causade and Sharpey (571), in their review, report 10 fatalities with doses from 10 to 30 grams. Assuming about 30 to 60 grams for an adult of 60 to 70 kilos, the median fatal dose of 45 grams (range 35 to 60 grams) of methyl salicylate, in the report of Wetzel and Nourse (273), would

TABLE 2  
*Toxic and fatal doses of the salicyl and canchophen groups in different species*  
 (Grams per kilo)\*

DRUG	AUTHOR AND REFERENCE NUMBER	MAN†	DOG	RABBIT	OTHER SPECIES
Salicyl group					
Acetylsalicylic acid	Block (160)	8-11, T, (R F) 7 5, T	0 2, T		300, T, horse 1 4, F, frog
	Dreser (40)		0 5-1, F, gastric		
	Barbour and Lozinsky (299)		0 5-0 8, F, vein	0 5-0 8, F, vein	
Amyl salicylate	Hanzlik (298)	8, T (R F) 8, T 10, F, infant† 45, F, adults§ 15, T, children**			15, F, guinea pig
Ethyl salicylate	Hanzlik and Prescho (21)				0 7, F, guinea pig
	Chanoz and Doyon (569)				
Methyl salicylate	Houghton (77)	1 3-1 4, T			
	Hanzlik (298)				
	Hanzlik and Prescho (24)				
Salicyl salicylate	Wetzel and Nourse (273)	5-6, T (R F) 9, T			
	Wetzel and Nourse (273)				
	Wetzel and Nourse (273)				
	Rocco (161)	3-4, T			
	Hanzlik (298)				
	Hanzlik and Prescho (23)				

Sodium salicylate	Blanchard (97) Waudswarth (206)	0.5-1, 1; 1, 1 in	0.5-1, 1; 1, 1 in 1 6, 1; 1; hypodermic	1, 1; 1; frog 0 4, 1; 1; cat; by post-mortem 0 6, emetic; cat 0 0 1 1, convuls absorbed 0 65 0 75; rat; convulsions
Strychnine salicylate	Cavalcade and Sharpes (511) Dreer (10)	12 20; **	1 1-1 6, convuls absorbed	1 1, 1; frog 0 05, 1; cat, very

## Chlorophenol group

Chlorophenol	Rothbarth (529) Wichour and Tordinsky (209)	0 6, 1; 1 25, 1; 1; rat tile 0 5, emetic; 1; rat tile	0 6, 1; 1 25, 1; 1; rat tile 0 5, emetic; 1; rat tile

\* Aberrations in the table have meanings as follows: 1, toxic symptoms of salicyllism; 2, fatal; and R 1, rheumatic fever, more than.

† Doses in this column are total doses the smaller doses, of those type cut as ranges are median doses for females, the larger doses for males; all others are median doses for males. These doses approach the minimal toxic doses, for in the majority of instances the administration had been pushed to, and then stopped at those of symptoms of salicyllism.

‡ The median of doses (40 to 15 cc.) causing severe toxicity in children up to 9 years reported in the paper of Wiedel and Nottme,

§ The median of doses (40 to 60 cc.) in adults reported in the paper of Wiedel and Nottme

\*\* Ten cases of fatal poisoning, presumably adults; not stated



TABLE 2—Continued

DRUG	AUTHOR AND REFERENCE NUMBER	MAN	DOG	RABBIT	OTHER SPECIES
Cinchophen group—Continued					
Cinchophen .....	{ Hanzlik, et al. (291) Starkenstein (320)	11, T.	1-2, paresis	0 5, delayed death; hypo- dermic	0 8 convulsive; frog, sodium cinchophen
Ethyl ester of cinchophen..	Miller and Boots (295)	11, T.			
Neocinchophen.....	{ Barbour and Lozinsky (299) Hanzlik, et al (291) Barbour, Lozinsky and Cle- ments (292)	15, T 10-16; (R. F.)	>50, gastric		

indicate that this ester and the sodium salt are about equally toxic

The fatal doses of cinchophen and its derivatives have been determined only to a limited extent, but, in general, cinchophen would seem to be about as toxic as sodium salicylate, though less than acetylsalicylic acid. Neocinchophen, according to Barbour and Lozinsky (299), would not seem to be fatal in any dosage, for a quantity of 250 grams, or  $\frac{1}{2}$  pound, was tolerated gastrically by dogs without ill effects

### *Clinical toxic dose*

This is also called the full therapeutic dose in rheumatic fever because the salicyl and cinchophen are administered until gastric and auditory disturbances supervene, i e., the symptoms of "toxicity," these coinciding with the full therapeutic benefit obtained. In a clinical statistical study of the toxicity of different salicylates in 400 patients, three-fourths of whom suffered with rheumatic fever, the median toxic doses for adult males and females, respectively, were found by Hanzlik (298) to be as follows: 180 and 140 grains (12 and 9.3 grams) of the synthetic sodium salicylate, 200 and 135 grains (13.3 and 9 grams) of the natural sodium salicylate, 120 (8 cc) minims of the methyl salicylate, 165 and 120 grains (11 and 8 grams) of acetylsalicylic acid, 100 and 83 grains (6.6 and 5.5 grams) of salicyl salicylate. For females the toxic dose was approximately 80 per cent of that for males. The toxic dose of salicyl salicylate was about 50 per cent of that of methyl salicylate and of acetylsalicylic acid about 60 per cent of that of sodium salicylate. The toxic dose of the synthetic sodium salicylate and methyl salicylate for about 68 per cent of individuals of both sexes was between 100 and 200 grains (6.6 and 13.3 grams). The toxic doses of the different salicylates was uninfluenced by age between 16 and 75 years, by racial differences, various disease conditions, and therapeutic response with the sodium salicylate. The median toxic doses of the different salicyl derivatives used by Hanzlik and Presho (see table 2) agree well with the statistical results. Individuals showed idiosyncrasy toward toxic doses of sodium salicylate, but no connection was found between this and such factors as age, sex, race and disease condition. Idiosyncrasy generally varied in the same patient, and was not influenced by previous salicylate

medication The range and distribution of the toxic doses of sodium salicylate will be seen from the curves in figure 12

According to Archambault (572), the toxic dose of salicyl in children is higher than would be calculated for the age In children as well as adults, MacLachlan (573) observed that it requires much smaller dose of salicyl salicylate than of sodium salicylate to produce toxic effects

The data on cinchophen are not extensive, but the reports of Hanzlik, Scott, Weidenthal and Fetterman (291), Barbour, Lozinsky and Clements (292) and Miller and Boots (295) indicate that the toxic

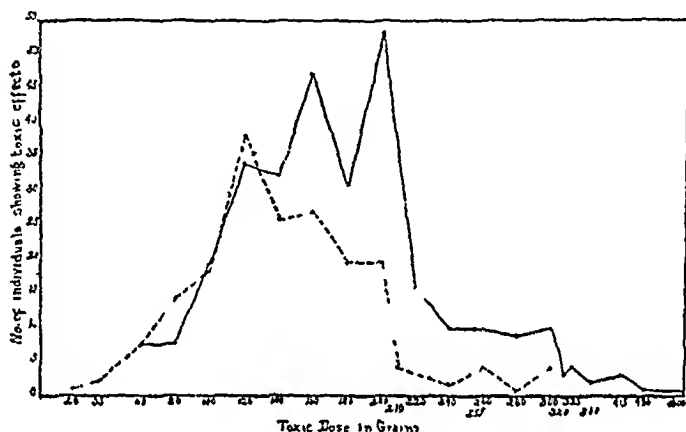


FIG 12 RANGE AND DISTRIBUTION OF FULL THERAPEUTIC OR "TOXIC" DOSES OF SODIUM SALICYLATE BASED ON CLINICAL STATISTICS

The continuous line represents males, the broken line, females

doses of cinchophen and its ethyl ester are about the same as that of sodium salicylate, i e , about 11 grams, and of neocinchophen approximately 40 per cent higher, i e , about 15 grams

### *Symptoms in animals*

In dogs, Bochefontaine and Chabbert (574) and Laborde (568) observed that an injection of 5 grams of sodium salicylate caused at first a slight acceleration of pulse and respiration and nausea, followed by efforts at vomiting, diarrhea, muscular depression, ataxia, dyspnea, general convulsions, circulatory collapse and death from asphyxia. The same was observed by Blanchier (97) in dogs, and this observer incidentally remarked that if the kidneys are diseased, elimination is

slow, and the accumulated salicyl will give rise to trouble. From experiments on animals, Chirone (575) concluded that the toxic action of salicylates is due to a more or less energetic decomposition of hemoglobin. According to See and Lahalle (361), the central nervous system is modified only by toxic doses, when sensation, motion and reflex movements disappear, and death is always preceded by convulsions. Quincke (576) reported the following symptoms, vomiting, dizziness, disturbance of sight, delirium and dyspnea, very large doses slowed the pulse and respiration, and the final picture ended up in collapse and cardiac paralysis. In experiments on rabbits, Charteris and McLennan (577) observed that injections of sodium salicylate caused circular and rotatory motions of the body with paresis and finally paralysis of the hind limbs, progressive prostration with complete muscular paralysis and death. The early symptoms described by Charteris and MacLennan were not observed by Waddell (296), and in rabbits, rats, and cats, the symptoms of intoxication by hypodermic injection of sodium salicylate were early vomiting (within 20 minutes), except those animals that cannot vomit (rodents), reflex excitability and convulsions, terminating in death from asphyxia in about 6 hours after acutely fatal doses, in 18 hours after just fatal doses. Chistoni and Lapresa (141) considered acetylsalicylic acid to be twice as toxic as sodium salicylate in dogs and rabbits, the greater toxicity being attributed to the acetyl radicle. Ethyl salicylate caused nausea and vomiting in guinea pigs, according to Houghton (77).

Toxic doses of cinchophen in frogs, mice, cats, dogs and rabbits were found by Starkenstein and Wiechowski (230) to cause mild convulsions and paresis, coma in dogs and cats. Intravenous injection in rabbits caused central vagus and vasomotor stimulation followed by depression, paralysis, fall of temperature, asphyxia and collapse. Rotter (578) reported that cinchophen was decidedly more toxic in cold blooded animals than in the warm blooded, causing central paralysis in frogs. Starkenstein (320) came to the conclusion that frogs, mice and rabbits were much less susceptible than cats and dogs, the symptoms of toxicity in the latter species being characterized by motor irritation and paralysis. Barbour and Lozinsky (299) found that 20 per cent suspensions (in acacia) of acetylsalicylic acid and cinchophen

were about 10 times more toxic than neocinchophen in rats, neocinchophen was also least toxic to dogs

### *Symptoms in man*

These are the same for salicyl and cinchophen and are characterized by deafness, ringing and buzzing in the ears, headache, nausea and vomiting, and sometimes diarrhea. With salicyl they were first observed by Stricker (426) and later reported by Peterson (579), Deseille (287), Hall (215), Tuckwell (582) and all subsequent observers. Delirium, mania and hallucinations after salicyl have been reported by Caussade and Sharpey (571), Dahy (580) and Krueg (581). Marshall (583) observed drowsiness with twitching of muscles and suppression of perspiration after 13.3 grams of sodium salicylate. According to Moore (286), nausea can be prevented by the addition of a few drops of chloroform to the salicylate. The toxic dose of strontium salicylate (12 grams) was found by Blankenhorn (584) to be the same as that of sodium salicylate, the symptoms being exactly the same and therapeutic efficiency no better.

Differences in sensitivity to salicylates were reported by Douglass-Hogg in 1877 (585). Richardson (586) cautioned against collapse after salicylic acid. Marked changes in respiration, great increase in pulse rate and collapse were reported by Wecherling (587). Undesirable side actions after 4 grams of sodium salicylate were reported by Lurmann (588). These consisted of a marked fall in temperature with shivering, and of edema of both extremities in a case of arthritis deformans. These effects occurred with repeated administration. Allaire (570) reported similar symptoms together with anuria and lessened secretion of saliva after 50 grams of sodium salicylate. Clayborne reported the presence of absolute scotomata in a patient made toxic with sodium salicylate. Besides the above symptoms, Langmead (590) reported the presence of acetone in the urine and breath of children poisoned with sodium salicylate and acetylsalicylic acid, 2 cases resulted fatally. Recently, Kiess (591) reported vomiting, pain and weakness in 3 subjects ranging from 5 to 22 years after the cutaneous application of 6 per cent salicylic acid in 95 per cent alcohol containing 15 per cent oil of cade. Two children, 5 and 7 years of age, died. These patients were treated for hypertrichosis and scabies and their

bodies were covered with the salicyl preparation. The deaths may have been due to other causes, but the other symptoms were unmistakable. A similar 2 per cent salicyl preparation gave nothing unusual in 200 other children.

An erythema has been frequently met with in the treatment of rheumatism with salicyl. This was reported by Heinlein (592), Erb (593), and Beier (594). Treufel (595) stated that erythema can be avoided by combining salicylates with hyperemia treatment, massage, and baths. Exanthema bullosum after the administration of 4 grams of sodium salicylate is reported by S. Rosenberg (596). There was burning of the skin with edematous swelling of lower eyelids, the face became bluish red and the entire body was covered with bluish red spots, after an additional dose of 7 grams bullae were formed, and a repetition of previous symptoms. Purpura following the administration of salicylate was reported by Ramond (597).

Lees (268) claimed that the administration of sodium bicarbonate with salicylate modified or prevented the appearance of symptoms of intoxication and even convulsions. However, this is not true, for all the symptoms of toxicity occurred in the human subjects of Hanzlik, Scott and Thoburn (339) and of Hanzlik, Scott and Reycraft (163) receiving bicarbonate. Moreover, bicarbonate and salicylate are routinely prescribed together in many quarters and the occurrence of symptoms of toxicity is well known. According to Meara (270), the use of alkalies with salicylates has been dictated more by tradition than by any rationale, and many side actions, such as retinal hemorrhages, are comparatively rare, and may be due to the disease rather than to the drug. A Lambert's (598) recommendation, in case a particular salicyl derivative produces unfavorable side actions, to try out others in turn until one is found which is favorably tolerated will give only partial success. It will succeed only with respect to a somewhat better taste and gastric tolerance of the less soluble derivatives. However, it does not avoid the symptoms of "toxicity" and possible side actions, for all the members of the salicyl and cinchophen group possess these in common, and, in rheumatic fever, full therapeutic efficiency and toxicity go hand in hand. It is futile to search for non-toxic, yet therapeutically efficient, substitutes or derivatives in this condition. Absence of toxicity means absence of therapeutic efficiency.

The post-mortem changes in fatal poisoning from sodium salicylate have been reported by Quincke (576) to consist of destruction of blood-corpuscles, congestion of most viscera and ecchymoses in serous membranes, cerebral hyperemia by Apolant (599). According to Baldoni (600), therapeutic doses of salicyl salicylate can produce changes in the blood, vessels and spleen. In the spleen a necrosis of the lymphoid elements of the malpighian bodies appeared. Vinci (345) reported nephritis, and in rabbits, Hanzlik and Karsner (341) demonstrated tubular nephritis.

Poisoning from methyl salicylate (oil of gualtheria) has occurred quite frequently, and at least 6 deaths are recorded in the literature. The symptoms are similar to those of poisoning from sodium salicylate, differing only in degree. In McNerthney's (601) case of fatal poisoning with oil of wintergreen in a child 3 years old, the symptoms consisted of nausea, vomiting, epigastric pain, slight opisthotonus, twitching of limbs, dilatation of pupils, rapid pulse, slow and labored respiration, hot and dry skin, and marked thirst. Wetzell and Nourse (273) have recently summarized a number of reports on this poisoning and report a case of their own of fatal poisoning in an infant 21 months old who swallowed 10 cc of pure oil of wintergreen. Marked ketosis was observed, and major nervous symptoms such as convulsions, chronic or toxic spasms of the extremities and hemiplegia. There were congestion and hemorrhages in viscera, especially multiple subserous hemorrhages of the heart, lungs and meninges, parenchymatous hemorrhages of the brain, lungs and kidneys, and extensive subdural hemorrhages. Other severe poisoning in children from 2 to 9 years have been reported by H. B. Myers (602), H. C. Wood (603), Gallaher (604), Hamilton (605), Stillé (606), and in adults by H. C. Wood (603), Jewett (607), Rosenbloom (271), Rosenbloom and Johnson (608), Legrain and Badonnel (609) and Emenheiser (610). Marked shortness of breath, or air hunger, is emphasized by the majority of reporters, also a semicomatose state, then coma, cyanosis and death. Recoveries among the adults have occurred from 30 cc, and fatalities, in 3 patients, from 30 to 55 cc. Chatin and Guinard (611) found the actions of methyl salicylate and methyl sodium salicylate to be identical. Baum (612) reported an amblyopia of five days' duration after large doses of the essence of wintergreen, Gibson and Felkin (613), excessive miosis and loss of light reflex.

The toxicity of the methyl salicylate is due partly to absorption of the unchanged ester. In the majority of cases of poisoning, the urines have smelled strongly of wintergreen. The excretion of the ester was discussed in the section on excretion. In the patients studied by Hanzlik and Presko (24), delayed and irregular absorption was characteristic. The absorption appeared to be delayed as much as 10 hours, and suggests that chemical antidotes and lavage would be valuable in the treatment of poisoning sometime after swallowing the ester. In Legrain and Brdonnel's case there was also a delay, no marked disturbance occurring during 10 hours. Since the cause of death is concerned with circulatory depression and cardiac paralysis as with other salicyl compounds, treatment would be directed at the circulations. All this means that the internal administration of the ester should be done cautiously, if at all, its use being preferably confined to external application.

Since the symptoms of cinchophen and its ethyl ester and neocinchophen are identical with those of salicyl, no further description is necessary. Hanzlik, Scott, Weidenthal and Fetterman (291) found them to be somewhat less frequent and pronounced with neocinchophen than with cinchophen in corresponding doses. The difference is only quantitative, however, and concerned with the poorer absorption and solubility of neocinchophen, for more pronounced and regular toxicity is obtainable with increased dosage. From the results of Miller and Boots (295), about the same holds true of the ethyl ester of cinchophen. As for side actions, the tendency to urticaria was found by Myers, Killian and Chace (293) to be more marked with cinchophen than with salicyl. The more marked gastric irritation with cinchophen than with neocinchophen has been mentioned previously. Besides gastric irritation, Schroeder (614) reported general itching, eruptions, edema, fever, headache, etc., after cinchophen in 17 patients. He advised administration of sodium bicarbonate, calcium as in exudative conditions, and liberal drinking of water with the drug to reduce and prevent these effects. Scully (615) reported an anaphylactoid reaction to cinchophen analogous to that from a foreign protein. Apparently many persons have a peculiar idiosyncrasy toward this drug as they have toward acetylsalicylic acid. Neocinchophen, according to Barbour, Lozinsky and Clements (292), appears to be a



rather inert drug as to side-actions, etc Oeller (447) claimed that the urine of patients receiving neocinchophen acquires a peculiar characteristic odor which is marked with large doses

*Idiosyncrasy to acetylsalicylic acid*

Hypersensitivity to small doses of this derivative is more common than to the other salicyl compounds It resembles the anaphylactoid phenomena, and is characterized by exudative features, suggesting an increased capillary permeability as the basis of the action, and in which the acetyl group appears to play an important part The mechanism is not understood, but it may be that the lipoid solubility, and, therefore, permeability, of this compound is better than that of sodium salicylate It will be recalled that it circulates unchanged in the body, and its toxicity is higher than that of sodium salicylate From their experiments in vitro indicating some reduced binding of free salicylic acid by serum of asthmatics hypersensitive to acetylsalicylic acid, discussed in the section on absorption, Van Leeuwen and Drzimal (124) claimed that the results indicated a higher concentration of the free drug in the blood exerting a more pronounced action than if it were bound After all, this does not explain the effects of acetylsalicylic acid, which exists in the circulation as the sodium salt, nor is it likely that the binding of added sodium salicylate would be the same as of salicylic acid

The following symptoms have been reported Constriction and edema in the throat with dysphagia and salivation by Otto (616), congestion in the nose, swelling of eyelids, edema of pharynx and salivation by Hirschberg (617), Gilbert (618), and Morgan (619) In Morgan's case, the diet contained fish and other preserved foods of animal origin, so that the urticaria and angioneurotic edema could be explained by this factor Congestion and edema of the pharynx with salivation and symptoms of choking with dysphagia after 5 to 10 grain (0.3 to 0.6 gram) doses have been reported by Macht (620) Edema of the eyelids and other symptoms of poisoning have been reported by Graham (621), Buhlig (622), after 10 grains (0.6 gram), Hansen (623), and Hearne (624) Kitchin (625) reported the case of a medical student who responded to 0.3 gram of acetylsalicylic acid at the end of 2 hours with severe angioneurotic swelling of the face

and arms, and to second, third and fourth doses with large urticarial wheals on the trunk and limbs and marked itching lasting 36 hours. After 1 gram, Sucin (626) observed swelling of the upper lip, the swelling soon extended to the entire head and was not relieved by cold applications, deglutition was painful and the pulse and respiration were increased. There seems to have been an unusual delay in the appearance of these symptoms. Berlioz (627) is the only one to claim that undesirable side actions are less common with acetylsalicylic acid than with sodium salicylate.

The death of a fetus as the result of the administration of salipyrin has been reported by Teilmann (628).

Proceeding on the assumption that the hypersensitivity to acetylsalicylic acid in their case was analogous to protein anaphylaxis, Widal and Vallery-Radot (629) claim desensitization of a patient, who had reactions to the drug 9 years, by the administration of the drug in increasing doses of from 0.005 to 0.03 gram at 1 hour intervals repeated 13 times during a period of 6 weeks. Labbe and Haguénau (630) proceeded along somewhat the same line, but claimed a kind of cross sensitization, perhaps from dietary articles. They desensitized by giving a small dose of the drug 1 hour before the full dose, the desensitization was temporary. However, the fundamental reasoning here is fallacious, for the peculiar reactions to acetylsalicylic acid occur in previously untreated (unsensitized) individuals, and, therefore, the condition does not correspond to protein sensitization. There would seem to be no doubt that, in such individuals, there is a pre-existing altered general functional state, probably in virtue of physical-chemical conditions in the cells and their media. It is peculiarly true that hypersensitive individuals give altered responses to a variety of agents physically and chemically different, and, therefore, there is nothing specific about it. The various aspects of the allergic state cannot be considered here, but a summary of the probable basis has been considered in a paper by Hanzlik (631).

Acetylsalicylic seems to partake of a narcotic action to some extent, as it appears to promote sleep in some individuals. Macht (632) reported habituation in an individual who consumed from 25 to 60 grains (1.6 to 4 grams) daily during 2 years for relief in pericostitis and osteitis. The habit grew from taking 5 grains (0.33 gram) for

relief of these conditions Constipation, digestive disturbances and low blood pressure were present

*"Natural" and synthetic salicylates*

Until 1911 to 1913, there was a belief among clinicians, practitioners and toxicologists that the salicylates made from some natural oil (as the oil of sweet birch) were less toxic than those prepared synthetically This idea has been particularly fostered by interested manufacturers Among the first to offer experimental evidence that the synthetic sodium salicylate might possess greater toxicity were Charteris and MacLennan (577) From two experiments on rabbits, they concluded that "natural" sodium salicylate was less fatal than the synthetic Later, Charteris (633) claimed to have established, in experiments on animals, that the greater toxicity of the synthetic salt was due to certain impurities (either accidentally or carelessly obtained during manufacture) such as cresotinic acids, particularly the paracresotinic acid Dunstan and Bloch (634) found ortho-, meta- and paracresotinic acids in specimens of synthetic salicylate and believed that this would explain the reported toxicities

Stokvis (635) claimed without convincing proof that the natural acid was less toxic than the synthetic because of its greater osmotic properties, this favoring elimination Many clinicians of Charteris' time were of the same opinion, however, not a single iota of evidence was offered by any of them that would definitely prove the greater toxicity of the synthetic salicylate A review of nearly all of the clinical papers on this phase of the question was made by Eggleston (636), who showed there was no definite or serious clinical or experimental evidence one way or the other

In 1890, Stockman (637) became suspicious of Charteris' experimental evidence and the claims of the older clinicians He objected to the statement that the toxic impurities in the artificial salicylate was cresotinic acid, because Buss (85) and Demme (638) had used it in place of sodium salicylate in treating children, and without observing any untoward symptoms May (461) stated that from 90 to 120 grains (6 to 8 grams) of *p*-cresotinic acid had been administered without producing toxic symptoms, and, from experiments conducted by himself, May concluded that the cresotinic acids resembled salicylic

acid as antifermentatives, bactericides, antipyretics, and they relieved rheumatic pain. The toxic effects in animals were about the same, although the ortho acid was more depressing to the circulation. This showed that if the synthetic salicylate contained an impurity no more toxic than the salicylate itself, the greater toxicity could not be attributed to the impurity. The experiments of Charters were repeated and extended by Waddell (296). Waddell could not confirm some of Charters' results, and showed definitely on cats, rats and rabbits that there were no demonstrable differences between the toxicities of the "natural" and synthetic sodium salicylates and the sodium paracresotinate. Mixtures of the paracresotinate and the different salicylates exhibited no greater toxicity than the components. The fatal and toxic doses obtained by Waddell have been already referred to, and these were practically the same for the different salicylates and the paracresotinate. Stockman (460) showed, in observations on patients, that the actions of sodium salts of the ortho-, meta- and paracresotinic acids did not differ from those of sodium salicylate.

Later clinical evidence supported these experimental observations on animals and patients. This was obtained from several clinicians in different parts of this country, who were unaware of the character of the salicylate, i.e., "natural" or synthetic, submitted to them for use in treatment of patients ill with rheumatic fever and otherwise. The results were summarized by A. W. Hewlett (639), who could find practically no difference in the toxic symptoms, size of dose or therapeutic responses with the salicylates of "natural" and synthetic origin. All of the reports were in uniform agreement. As to the validity of the claims for the existence of impurities in the "synthetic" salicylates from the chemical standpoint, the paper by Hilpert (16) may be consulted. This emphasizes the fact that salicylates of modern manufacture are practically free from impurities, and these include those of so called "inferior" as well as "superior" grades. In fact, the "natural" salicylate may contain more impurity than the synthetic. It must be concluded from all this that there are no demonstrable differences in the toxicities and therapeutic efficiencies of the "natural" and synthetic salicylates.

## METHODS OF ADMINISTRATION

*Oral*

This is the most common method used for administering salicyl and cinchophen and is efficient because nearly all the preparations are readily absorbed, the insoluble and unabsorbable compounds are rendered soluble and absorbable partly as such and partly after decomposition. Neocinchophen is so poorly soluble that it can be given only by mouth. There is no good reason why any other method should be generally adopted. Other methods do not avoid the emetic action, since this is central. Nausea from gastric irritation can be reduced by the administration of bicarbonate together with sodium salicylate or cinchophen. According to Weintraud (221), administration of bicarbonate together with cinchophen is indicated to prevent precipitation of urates in the urine. The salicyl derivatives are apt to cause quite as much gastric disturbance as ordinary salicylate. Neocinchophen appears to give the least disturbance, but its expense and the larger doses necessary for therapeutic effects outweigh the small advantages.

For headaches, colds, etc., single doses of from 0.5 to 1 gram of sodium salicylate or cinchophen are usually administered, 0.3 gram of acetylsalicylic acid, and about 1.5 grams of neocinchophen. In rheumatic fever, the intensive method is used and consists of administering 1 gram (or about 0.15 to 0.2 gram per kilo) of any of the members together with an equal quantity of bicarbonate every hour until symptoms of "toxicity" (salicylism) supervene. Then the administration may be stopped, and in many instances no further administration is necessary. Some prefer to continue the administration, using 1 gram 2 to 3 times daily for several days whether symptoms are present or not. Recurrence of the fever or other symptoms is always an indication for further administration. Salicylic acid should not be employed for internal administration on account of the marked gastric irritation. Lecoq (642) ascertained that as little as 0.69 gram of salicylic acid was not tolerated by infants and adults unless neutralized with bicarbonate.

### *Rectal*

This method has been advocated by Heyn (89) after experiences with 122 cases. The following advantages are claimed: (a) ease of administration, (b) ready absorption, (c) minimum of untoward effects, (d) easy removal of excess by enema, (e) results are more prompt than by other methods. The first adult dose consists of 8 to 10 grams of sodium salicylate dissolved in 120 to 180 cc of plain or starch water containing 1 to 1.5 cc of tincture of opium. This is repeated in 12 hours if symptoms of salicylism do not appear. The largest dose given was 24 grams. This would seem to have some advantages for children and for avoiding the taste and gastric irritation, but not toxicity. Irving (640) uses from 1 to 3 grains (0.06 to 0.2 gram) per pound of body weight, in starch paste or mucilage of acacia, once or twice daily in children to avoid gastric irritation. The latter is also testified to by Yague (641). The rectal method would be useful in case of anatomical defects of the upper alimentary tract.

### *Intravenous*

F. Mendel (643, 644) recommended the following solution in rheumatic fever, sodium salicylate 8 grams and caffeine sodium salicylate 2.5 grams dissolved in 50 cc of water. One-fourth of this solution (equivalent to 2 grams of sodium salicylate) is injected as a single dose in an adult, and this is repeated every twelve hours for three days or as often as necessary. The effects are prompt. Other advocates of intravenous salicyl therapy in rheumatic fever and other rheumatic affections are Lesné (645), who injects a 50 per cent solution of sodium salicylate using 0.25 gram for each year of the child's age, Lutembacher (646), who employs a 3.3 per cent solution and 3 grams of the salicylate twice daily, Gilbert, Coury and Benard (647), who inject from 0.25 to 2 grams, Matta (648), who uses 5 to 10 grams, Cernadas (649), who gives daily injections of 6 cc of a mixture of 5 grams sodium salicylate and 0.25 gram caffeine in 25 cc of water, and Carnot and Blamontier (526), who use from 4 to 6 grams daily and claim 1 to 3 grams sodium salicylate prevent involvement of the endocardium. The various advantages claimed by these advocates of the intravenous over other methods of administration, namely, the avoidance of gastric disturb

ance, emesis, and side actions in general, the prevention of cardiac involvement, and more rapid absorption and action are unsupported by a single iota of evidence. The various evidences that have been cited throughout disprove these claims. Absorption is rapid by mouth, the drug is not antiseptic and does not beneficially influence the endocarditis; the emesis is central and gastric irritation can be eliminated by the use of bicarbonate. There is, therefore, no good excuse for giving any of these drugs intravenously. In fact, when administered in that way they can cause considerable harm to the heart and other important organs, resulting in collapse. The object of the caffeine in some of the solutions is to correct or prevent the collapse action. Undesirable physical and chemical changes in the blood, and symptoms, in dogs injected intravenously with sodium salicylate have been demonstrated by Hanzlik, De Eds and Tanter (650), and a diminished permeability of the liver of dogs to rose bengal by Hanzlik and De Eds (651).

The same applies to the use of cinchophen intravenously. This has been used by B. Mendel (279) in the form of "leukotropin," a mixture of hexamethyleneamine and cinchophen, and in the form of "atophanyl," a mixture of equal parts of cinchophen and sodium salicylate containing procaine, by Sundermann (652) and Wessel (653), but is obviously polypharmaceutical and superfluous, if not dangerous.

### *Miscellaneous*

Hypodermic administration of sodium salicylate has been advocated by Behr (654) and Seibert (655), but strongly opposed by Brugsch (656) on the grounds that it is painful and gives no better, if as good, results as oral administration. No side actions occurred until about 5 grams of the drug were injected. The method is, of course, effective in animals. Intra-articular injection of sodium salicylate has been practiced by Santini (657), but is painful and the method is obviously limited by the inaccessibility of many joints. The cutaneous method is employed with salicylic acid and methyl salicylate in the form of an ointment, in oil or as liniment for local effects. For eczema and certain other dermatoses a plaster containing salicylic acid has been recommended by H. S. Klotz (658). The method is useless for securing systemic effects in the treatment of rheumatic fever because the absorption is irregular and inefficient.

## REFERENCES

## A REFERENCES USED IN THE TEXT

- (1) Reports on Public Health and Medical Subjects, No 23, Ministry of Health London, 1924
- (2) Public Health Reports, U S P H S, 1926, 41 113
- (3) TALLNER AND WHITE J Am Med Assoc, 1924, 83 425
- (4) DESMOULIÈRE J pharm chim, 1904 (6), 19 121
- (5) PIRIA Ann de chim et de phys, 1838, 69 298
- (6) LEROUX cit Petit Bull therap, 1876, 91 454
- (7) CAHOURS Ann de chim et de phys, 1844, 10 337, 13 90
- (8) KOLBE AND LAUTEMANN Ann d Chem u Pharm, 1860, 115 157
- (9) CAHOURS J de pharm et de chim, May 1843
- (10) WOHLGEMUTH, J Therap Monatshf, 1899, 13 276
- (11) DRESER Arch f ges Physiol, 1899, 76 306
- (12) New and Non-Official Remedies, 1925, published by American Medical Association, Chicago
- (13) GERLAND Chem Soc Quart Rev, 1852, 5 133
- (14) PROCTOR Am J Pharm, 1844, 45 241
- (15) BOURQUELOT Compt rend soc biol, 1894, 119 802, 1896, 122 1002
- (16) HILPERT J Am Med Assoc, 1913, 60 1137
- (17) SAVORRO Atti acad sci Torino, 1914, 48 948
- (18) FURUKAWA Chem Absts, 1919, 13 976
- (19) BECKER J Am Pharm Assoc, 1920, 9 520
- (20) LEECH M Am Med Assoc, 1922, 78 275
- (21) HANZLIK AND PRESHO J Pharm Exp Therap, 1923, 21 247
- (22) ALTWEGG U S Pat 1431, 863
- (23) HANZLIK AND PRESHO J Pharm Exp Therap, 1925, 26 61
- (24) HANZLIK AND PRESHO J Pharm Exp Therap, 1925, 26 71
- (25) GREENISH AND BEESLEY Pharm J, 1915, 94 201
- (26) HANZLIK AND WETZEL J Pharm Exp Therap, 1919, 14 25
- (27) DOEBNER AND GIESECKE Ann d Chem, 1887, 242 291
- (28) NICOLAÏER AND DOHRN Deutsch Arch f klin Med, 1903, 93 331
- (29) KOLBE J f prakt Chem, 1874, 10 89
- (30) FESER Arch f Therheilk, 1875, 1 53
- (31) MÜLLER, J J f prakt Chem, 1874, 10 444
- (32) SCHAEER, E J f prakt Chem, 1875, 12 123
- (33) MEYER AND KOLBE J f prakt Chem, 1875, 12 133, 178
- (34) NEUBAUER J f prakt. Chem, 1875, 2 1
- (35) BÉCHAMP Montpellier Méd, 1876, Jan, p 30, Feb, p 134
- (36) KOLBE J f prakt Chem, 1875, 11 9, 12 161
- (37) STODMAN Brit Med J, 1913, 1 597
- (38) FÜHNER Abderhalden's Handb der Biol Arbeits Abt., IV, 1923, Part 7, I
- (39) WATERMAN AND KUIPER Rec trav chim, 1924, 43 323
- (40) CORPENT Gior veneto disc med, Feb and March, 1876
- (41) KNOP J f prakt Chem, 1874 10 351
- (42) GARDER Science, 1924, 60 503



- (43) SALKOWSKI Berl klin Wochn, 1875, 12 297
- (44) IDEM Virchow's Arch f path Anat, 1899, 157 416
- (45) LESNIK Arch f exp Path Pharm, 1888, 24 167
- (46) USENER Zeit f Kind, 1913, 5 431
- (47) BUCHOLTZ Arch f exp Path Pharm, 1875, 4 1
- (48) CECI Zeit f physiol Chem, 1880, 4 373
- (49) KOCH Mitt a d Kaiserl Gesundheitsamt, 1881, 1 234
- (50) HEINZ Handbuch d exp Path u Therap, 1905, 1 181
- (51) WOOD, H D JR Univ Penn Med Bull, 1907, 19 312
- (52) BINZ Berlin klin Wochn, 1876, 13 385
- (53) FURBRINGER Berl klin Wochn, 1875, 12 249, Diss, Jena, 1875, No 8, pp 120,  
Centralb f d med Wissen, 1875, No 18, p 273
- (54) PRIDEAUX Practitioner, 1878, p 177
- (55) SOLLMANN J Am Med Assoc, 1908, 51 818
- (56) JORDAN Biochem J, 1911, 5 274
- (57) WOOD, H C JR Therap Gaz, 1911, 35 153
- (58) HODARA Monatschr f prakt Dermat, 1896, 23 117
- (59) BERKENBUSCH Therap Monatshf, 1915, 29 565
- (60) SAUERLAND Biochem Zeit, 1912, 40 56
- (61) DRESER Med Klin, 1907, 3 390
- (62) DRASCHE Wien, med Wochnschr, 1876, 26 1049
- (63) RANDOLPH AND DIXON Med News, 1885, 46 174
- (64) BOURGET Therap Monatshf, 1893, 7 531
- (65) LINNOISIER Lyon méd, 1895, No 3, p 84
- (66) SCHUMACHER Diss, Giessen, 1908
- (67) LEVIN, E Deutsch med Wochn, 1912, 38 2412
- (68) LINNOISIER AND LANNONIS Compt rend soc biol, 1896, 48 318
- (69) FLORET Deutsch med Wochn, 1902, 28 765
- (70) IMPENS Arch f ges Physiol, 1907, 120 1
- (71) JOACHIMOGLU Pharm Monatshf, 1924, 5 123
- (72) PLANELLES Arch exp Path Pharm, 1924, 104 272
- (73) KUZAYA Arch f exp Med, 1923, 1 75
- (74) BUROW Med Klin, 1911, 7 341
- (75) BREGUET Thèse de Gêneve, 1912, 119, abst, Chem Absts, 1913, 7 2255
- (76) EWALD Berl klin Wochn, 1889, 26 985
- (77) HOUGHTON Am J Physiol, 1905, 13 331
- (78) KUMAGAWA Virch Arch f path Anat, 1888, 113 134, 202, 394.
- (79) MASTBAUM Diss Munchen, 1889
- (80) PINCZOWER Therap Monatshf, 1910, 24 297
- (81) NENCKI Arch exp Path Pharm, 1886, 20 369
- (82) BONDZINSKI Arch exp Path Pharm, 1896, 38 88
- (83) WOOD, H C, AND HARE Therap Gaz, 1886, 12 73
- (84) BAAS Zeit f physiol Chem, 1890, 14 416
- (85) BUSS Berl klin Wochn, 1876, 13 445, 503 518
- (86) BARBOUR AND LOZINSKY J Lab Clin Med, 1923, 8 217
- (87) FIEDLER Diss Halle, 1905
- (88) MASSOL AND MINET Compt rend soc biol, 1908, 44 No 10
- (89) HEYN J Am Med Assoc, 1912, 43 1913, 1914, 44 1004

- (90) LENKO AND KRYZANOWSKI *Compt rend soc biol*, 1924, 90 307
- (91) FEHLING *Arch f Gynäk*, 1876, 8 298
- (92) OSWALD *Zeit f exp Path u Therap*, 1910, 8 226
- (93) HANZLIK *J Pharm Exp Therap*, 1912, 3 387
- (94) DE MUSSY *Bull de l'Acad de méd Paris*, 1877, 6 805
- (95) BÉNOIT *Thèse de Paris*, 1877, No 63
- (96) BÄLZ *Arch de Heilk*, 1877, 18 60
- (97) BLANCHIER *Thèse de Paris*, 1879, No 141
- (98) STOCKMAN *Brit Med J*, 1906, 2 1439
- (99) BERCKE *Zeit f Geburts u Frauenkr*, 1876, 1 477
- (100) ZWEIFEL *Arch f Gynäk*, 1877, 12 235
- (101) PAULI *Jahrh d Leist u Fortschr d ges Med*, 1879, 14 428
- (102) BERNARD, J AND LIVON, CH *Compt rend soc de biol*, 1878, 87 218
- (103) TACHAU *Arch exp Path Pharm*, 1911, 66 341
- (104) NENCKI *Arch exp Path Pharm*, 1895, 36 400
- (105) OLMER AND TIAU *Compt rend soc de biol*, 1910, 66 814
- (106) SUCK *Inaug Diss*, Dorpat, 1895
- (107) ROTKY *Zeit f klin Med*, 1912, 75 494
- (108) FILLIPPI *Clin med*, 1900, 6 No 7
- (109) VINCI *Arch farmacol sper Roma* 13 d 3, No 6, abstr *Biochem*, *Zentralbl*, 1904, 3 495
- (110) WHITHAM *Ophthalmoscope*, 1913, 2 71
- (111) ROSENBAACH AND POHL *Berl klin Wochn*, 1890, 27 813
- (112) LEUCH *Centralbl f klin Med*, 1890, 11 833
- (113) DEVOTO *Centralbl f klin Med*, 1891, 12 129
- (114) AULMONT cit WOOD, H C *Therapeutics*, 14th Ed, 1908, Lippincott, Phila
- (115) DOCK, G *Trans Mich Med Soc*, 1895, 19 494
- (116) ARMSTRONG AND GOODMAN *J Am Med Assoc*, 1911, 67 1553
- (117) GIFFORD, S R *Am J Ophthal*, 1922, 5 948
- (118) FILLIPPI AND NESTI *Allgem med Centralbl*, 1901, No 53, p 71
- (119) BONDI AND JACOBY *Hofmeister's Beitr z chem Phys u Path*, 1906, 7 514
- (120) FRÖHLICH AND SINGER *Arch exp Path Pharm*, 1923, 99 185
- (121) BONDI AND JACOBY *Arch exp Path Pharm*, 1924, 102 35
- (122) SCOTT, THORBURN AND HANZLIK *J Pharm Exp Therap*, 1917, 9 217
- (123) FIESSINGER AND DEBRAY *Compt rend soc biol*, 1922, 87 336
- (124) VAN LEEUWEN AND DRZIMAL *Arch exp Path Pharm*, 1924, 102 218, *Rec trav chim*, 1923, 42 736
- (125) CHABANIER, LEBERT AND LOBO-ONELL *Compt rend soc biol*, 1923, 88 178
- (126) IDEM *Ibid*, 1923, 33 608
- (127) COQUONIN *Compt rend soc biol*, 1922, 87 336
- (128) FRIEDRICHSEN *Arch exp Path Pharm*, 1917, 80 235
- (129) BI Z *Arch exp Path Pharm*, 1879, 10 147
- (130) KÖHLER *Centralbl f d med Wissensch*, 1876, No 32, p 553
- (131) TESER AND FRIEDBERGER *Berl klin Wochn*, 1875, 12 321, *Arch f Wissensch u prakt Therap*, 1875, 1, 2, 3, and 6
- (132) FLEISCHER *Centralbl f d med Wissensch* 1876, No 36, p 268
- (133) FARSKY *Sitzungs d Wien, Akad d Wissensch*, 1877, 74 49 *Centralbl f d med Wissensch*, 1877, No 13, p 238

- (134) MARMÉ *Nachrichten v d Ges d Wissensch*, Gottingen, 1878, 7 385
- (135) JACOBY *Biochem Zeit*, 1908, 9 532
- (136) EWALD *Arch f Physiol* (Dubois-Reymond), 1876, p 422
- (137) HANZLIK *J Pharm Exp Therap*, 1921, 17 385
- (138) BOOTS AND CULLEN *Proc Soc Exp Biol Med*, 1922, 19 287, *J Exp Med*, 1922, 36 405
- (139) POULSSON *Lehrbuch der Pharmakologie*, 1912, Ed 2, 249
- (140) GAZERT *Deutsch Arch f klin Med*, 1900, 68 142
- (141) CHISTONI AND LAPRESA *Arch di farmacol*, 1909, 8 63
- (142) BONDI AND KATZ *Zeit f klin Med*, 1911, 72 177
- (143) FILLIPPI *Arch di farmacol e terap*, 1907, 13 149
- (144) NEUBERG, C *Berl klin Wochn*, 1911, 48 798
- (145) BALDONI *Arch farm sper*, 1914, 17 241
- (146) NEMCKI *Arch f Anat u Physiol* (Phys Abt), 1870, p 399
- (147) WOLFFBERG *Deutsch Arch f klin Med* 1874, 15 403
- (148) FLEISCHER *Berl klin Wochn*, 1875, 12 529, 547
- (149) ROBIN *Gaz méd de Paris*, 1877, No 6, p 70
- (150) SÉE, G *Bull de l'acad de méd*, 1877, 6 689
- (151) SMITH-PYE *Brit Med J*, 1878, 1 293
- (152) POLLATSCHKE *Wien med Wochn*, 1888, 38 715
- (153) GEISSLER *Gaz méd*, 1877, Nos 7 and 8
- (154) CORNET *Progrès méd*, 1893, No 5, p 81
- (155) CHELCHOWSKI *Jahrb d Tierchem*, 1894, 24 296
- (156) PURPUS *Inaug Diss Erlangen*, 1898, cit Heffter *Ergebn d Physiol*, 1905, 4 256
- (157) BROUARDEL *Les empoisonnements criminels et accidentels*, Paris, 1902, p 104, cit Heffter *Ergebn d Physiol*, 1905, 4 256
- (158) EHRLMANN *Munch med Wochn*, 1907, 54 2595
- (159) HERISSEY, FIESSINGER AND DEBRAY *Compt rend soc biol*, 1922, 87 625
- (160) BLOCK *Inaug Diss*, Giessen, 1909, p 42
- (161) ROCCO *Arch di farmacol*, 1913, 13 567
- (162) HANZLIK, SCOTT AND THOBURN *J Pharm Exp Therap*, 1917, 9 247
- (163) HANZLIK, SCOTT AND REYCRAFT *Arch Int Med*, 1917, 22 1
- (164) HANZLIK AND WETZEL *J Pharm Exp Therap*, 1919, 14 43
- (165) MOSSO, U *Arch exp Path Pharm*, 1889, 26 267
- (166) THOBURN AND HANZLIK *J Biol Chem*, 1915, 23 163
- (167) HOLMES *J Pharm Exp Therap*, 1925, 26 297
- (168) WILEY U S Dept Agric, Bur Chem, Bull No 84, Part II, 1906
- (169) BALDONI *Arch di farm*, 1915, 18 151
- (170) DEVRIENT *Arch exp Path Pharm*, 1921, 90 242
- (171) CHISTONI *Arch intern de pharmacodynam et de therap*, 1924, 29 397
- (172) PITINI *Arch farm sper*, 1920, 29 113
- (173) BERTAGNINI *Ann d Chem*, 1856, 97 248
- (174) GNEHM *Ber*, 1875, VIII, 816, Report, Meeting Swiss Chem Soc, May 31, 1875
- (175) NEUBAUER AND VOGEL *Harnanalyse*, 1898, 3d ed, p 610
- (176) STOCKMAN *Edinburgh Med J*, 1906, Aug p 103
- (177) BALDONI *Chem Ztg*, 1905, 98 1273
- (178) BALDONI *Arch exp Path Pharm*, 1908, Supplementband, Schmiedeberg Festschrift

- (179) BALDONI Arch di farm sper e sc affini, 1914, 17 241
- (180) HANZLIK J Pharm Exp Therap, 1917, 10 461
- (181) BONDI Z f physiol Chem, 1907, 52 170
- (182) FISCHER, E Ber, 1909, 12 215
- (183) DRZIMAL Rec trav chim, 1924, 43 600
- (184) BALDONI Biochim terap sper, 1923, 10 271, 335
- (185) CIAMICIAN AND RAVENNA Gazz chim ital, 1920, 50 13
- (186) ANGELICO Arch farm sper 1921, 20 8
- (187) FALK, F Zeit f klin Med, 1910, 71 165
- (188) DORRN Zeit f klin Med, 1912, 74 445, Biochem Zeit, 1912, 43 240
- (189) SKORCZEWSKI AND SOHN Bull intern acad sci Cracovie, 1912, pp 885-7
- (190) GREINERT Arch exp Path Pharm, 1924, 77 458
- (191) SCHEUNEMANN Arch exp Path Pharm, 1923, 100 51
- (192) POHR Jahr f Tierchem, 1876, 6 188
- (193) WOLFSOHN Inorg Diss, Konigsberg, 1876
- (194) BLASSON J de therap, 1877, 19 721
- (195) CHIRONE AND PETRUCCI Commentario clin di Pisa, Jan and Feb, 1878
- (196) VIRCHOW, C Zeit f physiol Chcm, 1882, 6 78
- (197) SALOMÉ Med Jahrb d Gcsellsch der Acrzte in Wien, 1885, 4 463
- (198) JOLIN Skand Arch f Physiol, 1889, 1 442
- (199) TAUSZK AND VAS Ungar Arch f Med, 1892, 1 204
- (200) GOODEBODY J Physiol, 1900, 25 399
- (201) DENIS AND MEANS J Pharm Exp Therap, 1916, 8 273
- (202) OHTANI Osaka Med Soc, 1922, 21 No 11
- (203) MARROT Arch gén de med, 1879, 1 142
- (204) SCHREIBER AND WALDOVIGEL Arch exp Path Pharm, 1899, 42 69
- (205) HEPTER AND SMITH N Y Med J, 1892, 55 617
- (206) SIEGERT Münch med Wochn, 1897, 44 527, 561
- (207) HERRINGHAM AND DAVIES J Physiol, 1891, 12 475
- (208) MARTINEAU Bull gén de therap, 1876, 91 356
- (209) BOHLAND Centralbl f Inn Med, 1896, 17 70
- (210) HACK Inaug Diss, Bonn 1896
- (211) SCHREIBER AND ZAUDY Deutsch Arch f Klin Med, 1899, 62 242
- (212) LEWANDOWSKI Zeit f klin Med, 1900, 40 202
- (213) SINGER Arch f ges Physiol, 1901, 527
- (214) ULRICI Arch exp Path Pharm, 1901, 46 321
- (215) HALL Brit Med J, 1904, 2 744
- (216) ROCKWOOD Am J Physiol, 1909, 25 34
- (217) STOOKEY AND MORRIS J Exp Med, 1907, 9 312
- (218) WALCOMONT Arch intern pharmacodynam et therap, 1911, 21 369
- (219) POHL Biochem Zeit, 1916, 78 200
- (220) NAGASHIMA Acta Schol Med Kyoto, 1921, 4 257
- (221) WEINTRAUD Therap d Gegenwart, 1911, 52 97
- (222) PLEN Deutsch med Wochnsch, 1912, 38 103
- (223) RETZLAFF Ibid, 1912, 38 404, Zeit f exp Path, Therap, 1913, 12 307
- (224) SCHITTENHILF AND ULLMANN Zeit f exp Path u Therap, 1913, 12 360
- (225) WIECHOWSKI AND BASS Wien klin Wochn, 1912, No 47
- (226) ZUELZER Berl klin Wochnsch, 1911, 44 No 17

- (227) SKORCZEWSKI AND SOHN Zeit f exp Path u Therap , 1912, 11 254, Ibid, 1912, 11 501
- (228) KEHRER Arch f Verdauungs Krank , 1913, 19 98
- (229) BRUGSCH Berl klin Wochnsch , 1913, 40 No 34
- (230) STARKENSTEIN AND WIECHOWSKI Prager med Wochn , 1913, 38 36, Starkenstein Zeit f exp Path u Therap , 1911, 65 177
- (231) STARKENSTEIN Biochem Zeit , 1920, 106 129
- (232) PIETRULLA Deutsch med Wochn , 1913, 39 359
- (233) FOLIN AND LYMAN J Pharm Exp Therap , 1913, 4 539
- (234) DENIS J Pharm Exp Therap , 1915, 7 255
- (235) FOLIN AND DENIS J Biol Chem , 1913, 13 469
- (236) WEINTRAUD Therap Monatshf , 1912, 26 21
- (237) MCLESTER Arch Int Med , 1913, 12 739
- (238) STEINITZ Zeit f physiol Chem , 1914, 90 108
- (239) FRANK AND PIETRULLA Arch exp Path Pharm , 1914, 77 361
- (240) FINE AND CHACE J Pharm Exp Therap , 1914, 6 29
- (241) FINE AND CHACE J Biol Chem , 1915, 21 371, Proc Soc Exp Biol Med , 1915, 72 95
- (242) MYERS, KILLIAN AND SIMPSON Proc Soc Exp Biol Med , 1920, 17 187
- (243) MYERS AND KILLIAN J Pharm Exp Therap , 1921, 18 213, J Biol Chem Proc , 1921, 46 17
- (244) FINE AND CHACE Arch Int Med , 1915, 16 401
- (245) LEVI Biochim e terapia sper , 1922, 10 59
- (246) JOEL Zeit f klin Med , 1924, 100 170
- (247) HASKINS J Pharm Exp Therap , 1913, 5 63
- (248) HAWK AND SMITH Arch Int Med , 1915, 15 187
- (249) GRIESBACH AND SAMSON Biochem Zeit , 1919, 94 277
- (250) GRIESBACH Biochem Zeit , 1920, 101 172
- (251) GRAHAM Quart J Med , 1920, 14 10
- (252) WOLFF, A Biochem Zeit , 1925, 165 342
- (253) ROSENFELD Klin Wochn , 1924, 3 1908
- (254) GRABFIELD AND PRATT J Pharm Exp Therap , 1922, 19 261
- (255) ROTTER Zeit f exp Path u Therap , 1918, 19 176
- (256) BORAK Fortschritt auf d Gebiet der Rontgenstrahl , 1923, 31 2 98
- (257) GOLDWASSER Biochem Zeit , 1923, 143 323
- (258) STERN Biochem Zeit , 1924, 151 268
- (259) BAUMANN AND HERTER Zeit f physiol Chem , 1877, 1 244
- (260) MOREIGNE Centralbl f d med Wissen , 1900, No 39, p 658
- (261) KRAMER J Am Med Assoc , 1918, 71 783
- (262) SCHREUDER Maly's Jahrber u d Fortschr d Tierchem , 1889, 18 146, Diss , Utrecht, 1888
- (263) LACQUER Centralbl f Physiol , 1908, 22 717
- (264) MEYER, H H Arch exp Path Pharm , 1883, 17 304
- (265) WALTER Arch exp Path Pharm , 1877, 7 148
- (266) LEVY, ROWNTREE AND MARRIOTT Arch Int Med , 1915, 16 389
- (267) MARRIOTT Arch Int Med , 1916, 17 840
- (268) LEES Proc Roy Soc Med (Pharm Sec) , 1908-09, 2 34
- (269) DELORE J de Méd de Lyon, 1925, 6 259

- (270) MEARA Am J Med Sci, 1910, 139 328
- (271) ROSENDOOM J Am Med Assoc, 1919, 72 22
- (272) MYERS, H B J Am Med Assoc, 1920, 75 1783
- (273) WEITZEL AND NOURSE Arch Path Lab Med, 1926, 1 182
- (274) HURLEY AND TREVAN J Physiol, 1916, 50 Proc XLIX
- (275) COTTON Lyon mcd, 1877, 1 557
- (276) THIERSCH Volkmann's klin Vortr, 1875, Nos 84 and 85, p 637
- (277) PRUDDEN Am J Med Sc, 1882 (N S), 83 64
- (278) BINZ Arch exp Path Pharm, 1877, 7 275
- (279) MENDEL, B Deutsch med Wochn, 1922, 48 829, 1922, 48 1441
- (280) IKEDA J Pharm Exp Therap, 1916, 8 101
- (281) DOHRN Klin Wochn, 1923, 2 819
- (282) STARKENSTFEN Deutsch med Wochn, 1922, 48 1161
- (283) ULLMANN Zeit. f d gesamt exp Med, 1923, 32 319
- (284) SWIFT, MILLER AND BOOTS J Clin Investigation, 1924, 1 197
- (285) JACOBY AND SCHÜTZE Biochem Zeit, 1908, 9 527
- (286) MOORE N Y Med J, 1879, 30 1 and 113
- (287) DESEILLE Thèse de Paris, 1879, No 494
- (288) WEBER, F Allg med Centralbl, 1876, Mar 25, p 289
- (289) BENJAMIN, H Gaz mcd de Paris, 1877, 11 137
- (290) HELLEF Berl klin Wochn, 1911, 48 526
- (291) HANZLIK, SCOTT, WEIDENTHAL AND FETTERMAN J Am Med Assoc, 1921, 76 1728
- (292) BARBOUR, LOZINSKY AND CLEMENTS Am J Med Sc, 1923, 165 708
- (293) CHACE, MYERS AND KILLIAN J Am Med Assoc, 1921, 77 1230
- (294) MILLER AND BOOTS J Am Med Assoc, 1924, 82 1028
- (295) MILLER AND BOOTS J Lab Clin Med, 1924, 10 34
- (296) WADDELL Arch Int Med, 1911, 8 784
- (297) LECHESTON AND HATCHER J Pharm Exp Therap, 1915, 7 275
- (298) HANZLIK J Am Med Assoc, 1913, 60 957
- (299) BARBOUR AND LOZINSKY J Lab Clin Med, 1923, 8 217
- (300) MINAKOWSKI Therap der Gegenw, 1908, p 385
- (301) TOCCO-TOCCO Therap Monatshf, 1912, p 671
- (302) LEITCHENTRITT Zeit f physiol Chem, 1919, 104 154
- (303) STADFLMANN Therap Monatshf, 1891, 5 512, Berl klin Wochnschr, 1896, 33 181, 212
- (304) MANDELSTAMM Diss Dorpat, 1890, p 48
- (305) PFAFF AND BALCH J Exp Med, 1897, 2 49
- (306) DOMINIKIEWICZ Czasopismo lek, Lodz, 1908, 10 245
- (307) PIETROWA Zeit f physiol Chem, 1911, 74 429
- (308) SMYTH AND WHIPPLE J Biol Chem., 1924, 59 655
- (309) STRANSKY Biochem Zeit, 1925, 155 256
- (310) LEONE Arch farm sper, 1916, 22 377
- (311) LEONE Riforma med, 1916, 32 669
- (312) BRUGSCH AND HORSTERS Zeit f d gesamt exp Med, 1923, 38 267, Ibid, 1924, 43 517, Med Klin, 1924, 20 661
- (313) HORSTERS Arch exp Path Pharm, 1925, 105 51 (Proc)
- (314) GRUNENBERG AND ULLMAN Klin Wochn, 1924, 20 663

- (315) TESCHENBERG AND HOFMANN *Deutsch med Wochn*, 1925, 51 1611
- (316) SLOBOSIANO AND HERSCOVICI *Compt rend soc biol*, 1925, 92 1472
- (317) DIXON *Manual of Pharmacology*, 1915, 39, Arnold, London
- (318) ROCH *Rev med suisse rom*, 1922, 42 291
- (319) HERRISEY, FIESSINGER AND DEBRAY *Compt rend soc biol*, 1922, 87 625
- (320) STARKENSTEIN *Biochem Zeit*, 1920, 106 172
- (321) STARKENSTEIN *Zeit. f d gesamt exp Med*, 1924, 43 449
- (322) ALVAREZ *J Pharm Exp Therap*, 1918, 12 171
- (323) THIENES *Arch internat de pharmacodynam et de therap*, 1926 (in press)
- (324) BLANCHIER AND BOCHEFONTAINE *Compt rend soc biol*, 1878, 87 657
- (325) CARRIEU *Montpellier méd*, 1878, p 16, Feb
- (326) HUBER *Deutsch Arch f klin Med*, 1887, 41 129
- (327) CHOPIN *Bull gén de therap*, 1889, 58 119
- (328) BARDIER AND FRENKEL *Compt rend soc biol*, 1899, 51 147, 151, *J de physiol*, 1899, 1 463
- (329) SCOTT AND HANZLIK *J Am Med Assoc*, 1916, 67 1838
- (330) GEORGIEWSKY *Deutsch med Wochnschr*, 1911, 37 1030
- (331) STARKENSTEIN *Arch exp Path Pharm*, 1922, 92 339
- (332) OWEN *Brit Med J*, 1881, 2 1081
- (333) v ACKEREN *Charité Ann*, 1890, 15 253
- (334) LUTHJE *Deutsch Arch f klin Med*, 1902, 74 163
- (335) Kleinberger and Otenius *Deutsch Arch f klin Med*, 1904, 80 225
- (336) KNECHT *Munch med Wochnschr*, 1904, 51 956
- (337) BRUGSCH *Therap d Gegenw*, 1904, 45 58
- (338) MAMLOCK *Med Klin*, 1905, 1 523, 53
- (339) HANZLIK, SCOTT AND THOBURN *Arch Int Med*, 1917, 19 1029
- (340) FOLIN AND DENIS *J Biol Chem*, 1914, 18 273
- (341) HANZLIK AND KARSNER *Arch Int Med*, 1917, 19 1016
- (342) GLAESGEN *Munch med Wochnschr*, 1911, 58 1125
- (343) FREY *Munch med Wochenschr*, 1905, 52 1326
- (344) EISNER *Deutsch Arch f klin Med*, 1915, 118 125
- (345) VINCI *Arch d farm sper*, 1905, 4 59, *Biochem Zentralbl*, 1905, 4 240
- (346) QUENSTAEDT *Therap d Gegenw*, 1905, 46 97
- (347) TOCCO-TOCCO *Arch farm sper*, 1925, 39 42
- (348) SWIFT *Boston Med Surg J*, 1922, 187 331
- (349) CHATIN AND GUINARD *Compt rend Soc biol*, 1900, 52 669
- (350) CHANOS AND DOYON *Compt rend soc biol*, 1900, 52 716
- (351) TEISSIER AND GUINARD *J de Physiol et de Path Gén*, 1901, 3 42
- (352) DRISER *Therap Montsh*, 1903, 17 131
- (353) KOHLER *Centralbl f med Wissensch*, 1876, No 10, p 161, No 11, p 195
- (354) KOHLER *Deutsch Zeit f prakt Med*, 1877, 13 125, *Ibid*, 1878, 14 137
- (355) DANIEWSKI *Arb d Pharm Lab*, Moskau, 1876, 1 190
- (356) OLTAMARE *Thèse de Paris*, 1879, p 52
- (357) MARAGLIANO *Zeit f klin Med*, 1884, 7 248
- (358) ISTOMIN *Petersb med Wochnschr*, 1877, 40 341
- (359) ISTOMIN AND WELKY *Jahrb d Leist u Fortschr d ges Med*, 1878, 1 407
- (360) BORRISOW *Russ Vrach*, 1913, 12 241
- (361) SÉE AND LAHALLE *cit Deseille Thèse de Paris*, 1879

- (362) MARAGLIANO *Centralbl f d med Wissensch*, 1882, No 48, p 865
- (363) Faval *Thèse de Lyon*, 1887
- (364) SALANT AND JOHNSON *Proc Soc Exp Biol Med*, 1923, 20 390
- (365) OFUSHIMA *Acta Schol Med Kyoto*, 1920, 3 667
- (366) OKUSHIMA *Acta Schol Med Kyoto*, 1922, 5 1
- (367) MENDENHALL AND CAMP *Boston Med Surg J*, 1924, 190 312
- (368) POHL *Zeit f exp Path Ther*, 1918, 19 198
- (369) WIECHOWSKI *Arch exp Path Pharm*, 1903, 48 397
- (370) KONDO *Jap Med Lit*, 1919, 4 18
- (371) LIVON *Marseilles méd*, 1890, 27 3
- (372) SCHÜLLER *Arch exp Path Pharm*, 1925, 106 265, *Arch exp Path Pharm*, 1925, 105 XIII (Proc), *Ibid*, 1926, 111 33 (Proc)
- (373) MATTOZ *Gaz med de Rio Janeiro*, 1905, No 9, cit *Zentralbl f Biochem u Biophysik*, 1906, 4 633
- (374) PULLMANN *Berl klin Wochenschr*, 1889, p 604
- (375) SCHUCHARDT *Corr Blatt d arzt Ver Thüringen*, 1886, No 7
- (376) WACKER *Centralbl f Gynak*, 1889, p 685
- (377) LYNHART *Ibid*, 1890, p 438
- (378) BINZ *Berl klin Wochenschr*, 1893, 30 985
- (379) GUNN AND GOLDBERG *J Pharm Exp Therap*, 1922, 19 207
- (380) KIRCHNER *Berl klin Wochenschr*, 1881, 18 725, *Monatschr f Ohrenheilk*, 1883, 17 85
- (381) Blau *Zeit f Ohrenheilk*, 1903, 45 No 4, *Arch d Ohrenheilk*, 1904, 61 220
- (382) HAIKE *Arch f Ohrenheilk*, 1904, 63 78
- (383) WITTMARK *Centralbl f d med Wissensch*, 1903, No 30, p 509, *Arch f d ges Physiol*, 1903, 95 209
- (384) LINDT *Corr Blatt f schweiz Aerzte*, 1914, 43 1444
- (385) BEREZIN *Abst J Am Med Assoc*, 1916, 67 844
- (386) JUSTI *Centralbl f Chir*, 1876, p 629, *Deutsch med Wochenschr*, 1876, 2 259
- (387) GOLTDAMMER *Berl klin Wochenschr*, 1876, 13 47
- (388) WOOD, H C *Therapeutics*, Ed 11, Philadelphia, 1902
- (389) BUSS *Diss*, Basle, 1875, *Arch f klin Med*, 1875, 15 457, *Stuttgart*, 1878, *Monograph*, pp 246
- (390) HARDISAR *J Pharm Exp Therap*, 1924, 23 395
- (391) BARBOUR AND HERRMANN *J Pharm Exp Therap*, 1921, 18 165
- (392) MORIMAKA *Zeit f physiol Chem*, 1923, 129 111
- (393) HASHIMOTO *Arch exp Path Pharm*, 1915, 78 394
- (394) WOOD AND REICHERT *J Physiol*, 1882, 3 321
- (395) STUHLINGER *Arch exp Path Pharm*, 1900, 43 166
- (396) LIVON *Compt rend acad d sc*, 1880, 90 321
- (397) YOSHINAGA *Mitt a d med Fak Kyushu Univ*, 1925, 10 161
- (398) NITZESCU AND COSMA *Compt rend soc biol*, 1923, 89 1106
- (399) YAMAMOTO *Kyoto Igaku Zasshi*, 1918, 15 115 *Chem Absts* 1919, 13 1342
- (400) STARKASTFIN *Therap Monatskf*, 1917, 31 19
- (401) DITTRICH *Zeit f ges exp Med*, 1924, 43 270
- (402) HILSE *Arch exp Path. Pharm*, 1925, 105 XIII (Proc)
- (403) RIESS *Berl klin Wochenschr*, 1875, 12 673, 670
- (404) RIEGEL *Berl klin Wochenschr*, 1876, 13 181



- (405) GEDL Centralbl f d med Wissensch , 1876, No 23, p 403
- (406) MOELI Deutsch Arch f klin Med , 1876, 17 592
- (407) HARE Therap Gaz , 1887, 11 444
- (408) BARBOUR AND DEVENIS J Pharm Exp Therap , 1919, 13 499, Arch Int Med , 1919, 29 617
- (409) ZIMMERMANN Arch exp Path Pharm , 1875, 4 248
- (410) BARBOUR Physiological Reviews, 1921, 1 295
- (411) BARBOUR J Pharm Exp Therap , 1919, 13 500 Arch Int Med , 1919, 24 624
- (412) ZIMMER Zeit f d gesamt exp Med , 1923, 32 217
- (413) WOLFBERG Deutsch Arch f klin Med , 1875, 16 162
- (414) PEL, P K Deutsch Arch f klin Med , 1876, 14 428
- (415) NATHAN DISS , Kiel, 1875, Centralbl f d med Wissensch , 1876, No 11, p 204
- (416) JOHANSEN, CH H DISS , Berlin, 1875, Centralbl f d med Wissensch , 1876, No 5, p 91
- (417) HILLER Deutsch Arch f klin Med , 1875, 16 614
- (418) FISCHER Deutsch Zeit f prakt Med , 1875, No 50, p 433
- (419) BUTT Centralbl f d med Wissensch , 1875, No 18, p 276
- (420) ROSENTHAL DISS , 1875
- (421) HILDEBRANDT Deutsch med Wochenschr , 1876, 2 289
- (422) JAHN Deutsch Arch f klin Med , 1877, 18 400
- (423) THOMAS, J P Phila Med Surg Rep , 1877, 36 22
- (424) RAMOND AND SCHULTZ Bull de la soc med et Hop , 1916, 22 866
- (425) BONDI Zeit f klin Med , 1911, 72 171
- (426) STRICKER Berl klin Wochnschr , 1876, 1 15, 99, Deutsch militärartzl Zeit , 1877, 1 1
- (427) KATZ Deutsch med Wochnschr , 1876, 2 48
- (428) MELTZER, O Munch med Wochnschr , 1909, 56 1800
- (429) PETIT Bull gén de thérap , 1876, 91 454, 508
- (430) BROADBENT Lancet, 1876, 1 254
- (431) SCHUMACHER Deutsch med Wochnschr , 1876, 2 208
- (432) STEINITZ Allg med Centralbl , 1876, Mar 4, p 217
- (433) v IBEEL Deutsch med Wochnschr , 1877, 3 477, 501
- (434) OETTINGER Wien med Presse, 1877, p 34
- (435) CAVAFY St George's Hosp Rep , 1877, 8 198
- (436) VULPIAN, J J pharm et chim , 1880, 55 (1) 373, 477, (2) 435
- (437) HALL Lancet, 1881, 2 1081
- (438) REIHLEN Munch med Wochnschr , 1886, 33 365
- (439) AUFRECHT Deutsch med Wochnschr , 1888, 14 23
- (440) FRASER Edinburgh Med J , 1885, 31 1
- (441) HANZLIK, SCOTT AND GAUCHAT J Lab Clin Med , 1918, 4 112
- (442) SWIFT Am J Med Sci , 1925, 170 631
- (443) MILLER, J L J Am Med Assoc , 1914, 63 1107
- (444) GORDON Virginia Med Semi-Monthly, 1910, 14 572
- (445) KLAIVENESS St Paul Med J , 1910, 12 371
- (446) OELLER Zentralbl f inn Med , 1916, 37 874
- (447) OELLER Med Klin , 1912, 8 2029
- (448) BENDIX Therap d Gegenw , 1912, 53 301
- (449) NEUKIRCH Therap Monatshf , 1912, 26 645

- (450) KLEMPERER *Therap d Gegenw*, 1913, 54 257
- (451) JOEL *Prag med Wochnschr*, 1913, 38 465
- (452) HAHN *Prag med Wochnschr*, 1913, 38 728
- (453) BEECK *Deutsch med Wochnschr*, 1916, 42 484
- (454) FRIDBERG *Fortschr d Med*, 1913, 31 318
- (455) COCKayne *Quart J Med*, 1911, 4 336
- (456) BINZ, C *Pharmacology for Practitioners and Students*, trans by Latham, 1897,  
Vol II No New Sydenham Soc, London
- (457) BERTRAM *Brit Med J*, 1925, 1 492
- (458) CHRISTROM AND WAHLBERG *Acta med Scand*, 1923, 58 350
- (459) SHERWIN *J Biol Chem*, 1918, 36 309
- (460) STOCKMAN *J Pharm Exp Therap*, 1912, 4 97
- (461) MAY *Brit Med J*, 1909, 2 791
- (462) DEMME *Therap Monatshf*, 1890, 4 191
- (463) SWIFT *J Am Med Assoc*, 1920, 74 1668
- (464) SWIFT *J Exp Med*, 1922, 36 735
- (465) DAVIS *Arch Int Med*, 1915, 15 555
- (466) TANTUS, SIMMONDS AND MOORE *Arch Int Med*, 1917, 19 529
- (467) SIMMONDS AND MOORE *Arch Int Med*, 1916, 17 78
- (468) SIMMONDS AND MOORE *Arch Int Med*, 1917, 19 153
- (469) SWIFT AND BOOTS *J Exp Med*, 1923, 37 553
- (470) HUTYRA AND MAREK *Spezielle Pathologie und Therapie der Haustiere* 1910,  
Ed 3, Fischer, Jena
- (471) STARKENSTEIN *Therap Monatshf*, 1917, 31 189
- (472) STARKENSTEIN *Therap Monatshf*, 1918, 32 289
- (473) STARKENSTEIN *Munch med Wochnschr*, 1919, 66 205
- (474) HIRSCHFELDER *Am J Physiol*, 1924, 75 507
- (475) TANTER AND HANZLIK *J Pharm Exp Therap*, 1924, 24 179
- (476) HANZLIK *Calif and West Med*, 1926, 24 33
- (477) JANUSCHKE *Wien klin Wochnschr*, 1913, 26 869
- (478) DOHRN *Therap d Gegenw* 1913, 54 196
- (479) HUBNER AND GILDEMEISTER cit Lacquer and Magnus *Zeit f d gesamt. exp  
Med*, 1921, 13 200
- (480) GUERST *Arch exp Path Pharm*, 1925, 105 238
- (481) LACQUER, E AND MAGNUS, R *Zeit f d gesamt exp Med*, 1921, 13 200
- (482) HANZLIK AND TANTER *J Lab Clin Med*, 1923, 9 166
- (483) ROSENTHAL AND WIDAL *Bull de l'Acad de med Paris*, 1910, 64 8
- (484) MILLER, J L AND IUSK, F B *J Am Med Assoc*, 1916, 67 2010
- (485) CECIL *Arch Int Med*, 1917, 20 951
- (486) SCULLA *J Am Med Assoc*, 1917, 69 20
- (487) MENZER *Med Klin*, 1922, 18 1022
- (488) GREGORY *Brit J Child Dis*, 1924, 21 131
- (489) BAUER *Wien klin Wochnschr*, 1923, 36 256
- (490) ROCH AND KATZENELLENBODGEN *Annal d Med*, 1923, 12 463
- (491) KAESSE *Zeit f Chir*, 1924, 183 316
- (492) MASALONGO *Atti ist Veneto*, 1919, 76 637
- (493) VIOLA *Polichinco*, 1921, 28 1235
- (494) GIROUX *Les Rhumatismes Aigus et leur Traitement*, 1923, pp 92, Baillière et fils,  
Paris

- (495) BLUMENTHAL *Med Klin*, 1921, 17 786
- (496) MARTONE *Gazz d Osp ed Chir*, 1915, 36 129
- (497) WIDAL *Nouveau Traité de méd et de Thérap*, 1912, pp 162, 6th Ed, Baillière et fils, Paris
- (498) LAMPRONTI *Riforma med*, 1921, 37 225
- (499) HOPPE *Berl klin Wochnschr*, 1919, 56 1040
- (500) EHRLICH *Zeit f physiol Chem*, 1906, 47 173
- (501) ROLLY *Der Akute Gelenkrheumatismus*, 1920, pp 177, Springer, Berlin
- (502) TOPLEY AND WEIR *J Path Bact*, 1921, 24 333
- (503) RIESMAN *J Am Med Assoc*, 1921, 76 1377
- (504) BOOTS AND SWIFT *J Am Med Assoc*, 1923, 80 12
- (505) SWIFT *J Exp Med*, 1924, 39 497, *J Am Med Assoc*, 1924, 82 1640 (Proc)
- (506) TURNBULL *J Am Med Assoc*, 1924, 82 1757
- (507) VAUGHAN *J Lab Clin Med*, 1924, 9 354
- (508) MACCALLUM *Bull Johns Hopkins Hosp*, 1924, 35 329
- (509) SWIFT, ANDREWS AND DERRICK *J Am Med Assoc*, 1925, 84 1952 (Proc)
- (510) STOCKMAN *Proc Roy Soc Med*, 1908, 2 31
- (511) MILLER, R *Quart J Med*, 1913, 6 519
- (512) ZADEK *Therap d Gegenw*, 1915, 56 251, 297
- (513) FRENKEL *Praktichewsky Vrach*, 1916, 15 278
- (514) LIBARONA *Sem Méd*, 1924, 1 347
- (515) KUNZE, C F *Deutsch Zeit f prakt Med*, 1876, No 28, p 323
- (516) MARK *J Metab Res*, 1924, 4 135
- (517) FRASER *Edinburgh Med J*, 1882, 2 1132
- (518) WAGNER *J f prakt Chem*, 1875, 11 57
- (519) SICK *Munch med Wochnschr*, 1912, 59 1605
- (520) EBSTEIN *Deutsch med Wochnschr*, 1911, 37 1476
- (521) EBSTEIN AND MULLER *Berl klin Wochnschr*, 1876, 13 337
- (522) v BRINKEN *Deutsch med Wochnschr*, 1877, 3 469
- (523) MULLER-WARNEK, G *Berl klin Wochnschr*, 1877, 14 43
- (524) FURBRINGER *Deutsch Arch f klin Med*, 1878, 21 476
- (525) KAUFMANN *Zeit f klin Med*, 1903, 48 260
- (526) CARNOT AND BLAMONTIER *Paris méd*, 1925, 27 477
- (527) DENECHAU AND BARBARY *Bull soc med Hop*, 1925, 49 1199
- (528) EHRLICH, H *Med Klin*, 1924, 20 643
- (529) RICHARTZ *Deutsch med Wochnschr*, 1913, 39 953
- (530) CULLEN *J Am Med Assoc*, 1898, 30 1218
- (531) DEUTSCH *Munch med Wochnschr*, 1911, 58 2652
- (532) ZUELZER *Berl klin Wochnschr*, 1911, 48 2101
- (533) MEIDNER *Therap d Gegenw*, 1912, 53 164
- (534) NEILSON *U S Naval Med Bull*, 1921, 15 259
- (535) EDITORIAL *Calif and West Med*, 1926, 29 384
- (536) SCHUSTER *Diss*, Erlangen, 1878
- (537) DEMETEVILLE *Rev med de la Suisse Rom*, 1925, 45 321
- (538) WUNDERLICH *Arch d Heilk*, 1876, No 5, p 470
- (539) HOFFMANN, L *Berl klin Wochnschr*, 1876, 13 494
- (540) LUTZE *Therap Monatshf*, 1893, 7 340
- (541) FIORINI *Gazz degli Osp e dell Clin*, 1917, 38 680

- (542) HIRSCHBERG Therap Monatshf, 1912, 26 721
- (543) KÖSTER Therap Monatshf, 1892, 6 117
- (544) LEONHARD ASTER Deutsch Zeit f prakt Med, 1876, 33 367
- (545) SMITH, E Am J Pharm, 1911, 83 390
- (546) SEBRING Med Rec, N Y, 1899, 55 558
- (547) SMITH, J F Brit J Derm Syph, 1925, 37 33
- (548) MALONEY Arch Derm Syph, 1924, 9 752
- (549) BERTHOLD Bull de thérp, 1876, 41 247
- (550) ROCH Bull gén de thérp, 1912, 163 218
- (551) IMPALLOMNI Chirurg d Organ di Movimento, 1917, No 3, p 380
- (552) BRAHN Münch med Wochnschr, 1923, 70 209
- (553) GIFFORD, H J Am Med Assoc, 1900, 34 341, Trans Ophth Sec Am Med Assoc, 1899, Ophth Rec, 1902, The Ophthalmoscope, 1910, 8 257
- (554) WELTON Arch f Ophth, 1911, p 379
- (555) BAYE Arch f Ophth, 1900, p 451
- (556) CAMPBELL Ophth Rec, 1908, p 581
- (557) DE SCHWEINITZ Diseases of the Eye, 1895
- (558) WOOD, C System of Ophth Therap, 1909, p 521
- (559) WEBSTER Ophth Rec, 1909, p 521
- (560) BAKER Ophth Rec, 1909, p 522
- (561) HEUSE Centralbl f prakt Augenheilk, 1901, p 111
- (562) LINDAHL Ophthalmoscope, 1905, 3 195
- (563) WIDMARZ Mitt a d Augenhk, Stockholm, 1908, 9 111
- (564) MOULTON J Am Med Assoc, 1920, 75 725
- (565) CAMPBELL J Am Med Assoc, 1921, 77 1223
- (566) DUNBAR Brit Med J, 1925, 1 14
- (567) GRZYWA Zeit f Chir, 1925, 52 1017
- (568) LABORDE Bull gén de therap, 1877, 93 276
- (569) CHANOT AND DOYO Lyon méd, 1900, No 31, p 487
- (570) ALLAIRE L'Union méd, 1879, 27 1014
- (571) CAUSSADE AND SHARPEY Rev de Med, 1921, 38 127
- (572) ARCHAMBAULT, 1878 cit Deseille, Thèse de Paris, 1879, No 494
- (573) MACLACHLAN J Am Med Assoc, 1913, 61 116
- (574) BOCHÉPONTAINE AND CHABBERT Compt rend soc biol, 1877, 85 575
- (575) CHIRONE Jahrb d Leist U Fortschr d ges Med, 1878, 1 407
- (576) QUINCKE Berl klin Wochnschr, 1882, 19 709
- (577) CHAPTERIS AND MCLENNAN Brit Med J, 1889, 2 1208
- (578) ROTTER Zeit exp Path Therap, 1918, 19 176
- (579) PETERSON Deutsch med Wochnschr, 1877, 3 13, 29
- (580) DAHY Brit Med J, 1878, 1 87
- (581) KRUEG Wien med Presse 1886, 27 406
- (582) TUCKWILL Lancet, 1876, 2 20
- (583) MARSHALL Brit Med J, 1877, 1 229
- (584) BLANKENHORN J Am Med Assoc, 1916, 66 331
- (585) DOUGLASS HOGG Thèse de Paris, 1877, 4 103
- (586) RICHARDSON Phila Med Times, 1876, p 391
- (587) WICKERLING Deutsch Arch f klin Med, 1877, 19 319
- (588) IURMAN Berl klin Wochnschr, 1876, 13 477

- (589) CLAYBORNE Trans Ophth Soc, 1906, 10 3
- (590) LANGMEAD Lancet, 1906, 1 1822
- (591) KIESS Therap d Halbmonatshf, 1921, 14 433
- (592) HEINLEIN Bayer artzl Intelligenzbl, 1878, 15 145
- (593) ERB Berl klin Wochnschr, 1884, 21 445
- (594) BEIER Arch f Dermat u Syph, 1894, 28 125
- (595) TREUFEL Munch med Wochnschr, 1907, 54 1931
- (596) ROSENBERG, S Deutsch med Wochnschr, 1886, 12 569
- (597) RAMOND Progrés méd, 1904, p 471
- (598) LAMBERT, A J Am Med Assoc, 1911, 57 898
- (599) APOLANT Berl klin Wochnschr, 1881, 18 82
- (600) BALDONI Arch di Farmacol, 1913, 14 377
- (601) MCNERTHNEY Northwest Med, 1903, 1 495
- (602) MYERS, H B J Am Med Assoc, 1920, 75 1783
- (603) WOOD, H C Therap Gaz, 1878, 2 76
- (604) GALLAHER Phila Med Examiner, 1852, 8 347
- (605) HAMILTON N Y Med J, 1875, 21 602
- (606) STILLÉ Materia Medica, 1860, p 593
- (607) JEWETT N Y Med Gaz, 1867, 1 380
- (608) ROSENBLUM AND JOHNSTON J Am Med Assoc, 1918, 72 26
- (609) LEGRAIN AND BADONNEL Paris Letter, J Am Med Assoc, 1922, 78 1140
- (610) EMENHISER U S Naval Med Bull, 1925, 22 697
- (611) CHATIN AND GUINARD Lyon méd, 1900, 94 480, 511.
- (612) BAUM Clinique Ophth, 1904, No 3
- (613) GIBSON AND FELKIN Practitioner, 1889, 42 17
- (614) SCHROEDER Ugesk f Laeger, 1922, 84 1141
- (615) SCULLY J Am Med Assoc, 1924, 82 623
- (616) OTTO Deutsch med Wochnschr, 1903, 29 123
- (617) HIRSCHBERG Deutsch med Wochnschr, 1902, 28 416
- (618) GILBERT J Am Med Assoc, 1911, 56 1262
- (619) MORGAN, C Brit Med J, 1911, 1 307
- (620) MACHT Med Rec, 1911, 80 826
- (621) GRAHAM J Am Med Assoc, 1911, 56 221
- (622) BUHLIG Quart Bull Northwestern Univ, Dec 1911
- (623) HANSEN Ugesk f Laeger, 1924, 86 249
- (624) HEARNE Brit Med J, 1920, 2 418
- (625) KITCHIN J Am Med Assoc, 1920, 74 889
- (626) SUCIN Foreign Letters, J Am Med Assoc, 1924, 83 1522
- (627) BERLIOZ L'Union pharm, 1903, p 97
- (628) TEILMANN Hospitalstid, 1910, 53 No 9
- (629) WIDAL AND VALLERY-RADOT Presse méd, 1920, 28 93
- (630) LABBÉ AND HAGUENAU Presse méd, 1921, 29 761
- (631) HANZLIK J Am Med Assoc, 1924, 82 200
- (632) MACHT Med Rec, 1918, 94 767
- (633) CHARTERIS Brit Med J, 1891, 1 695
- (634) DUNSTAN AND BLOCH Pharm J and Trans, 1890-91 (3), 21 429
- (635) STOKVIS Wien med Presse, 1894, 35 1209, Atti d XI Cong med internatz, 1894, 3 90

- (636) EGGLESTON J Am Med Assoc, 1912, 59 2057
- (637) STOCKMAN Brit Med J, 1890, 2 1271
- (638) DEMME Med Chir Centralbl, 1888, 23 243
- (639) HEWLETT, A W J Am Med Assoc, 1913, 61 319
- (640) IRVING Arch Ped, 1923, 40 832
- (641) YAGUE Arch Españ de Enf del Op Dig, 1918, 1 501
- (642) LECOQ Bull sci pharmacol, 1915, 22 84
- (643) MENDEL, F Therap Monatshef, 1904, 18 165
- (644) MENDEL, F Münch med Wochnschr, 1905, 52 165
- (645) LESNÉ Bull soc Pediat de Paris, 1922, 5 201
- (646) LUTEMBACHER Presse méd, 1921, 29 895
- (647) GILBERT, COURV AND BÉVARD Compt rend soc biol, 1921, 85 421
- (648) MATTA J Am Med Assoc, 1916, 67 1979
- (649) CERNADAS Semana med, 1915, 22 No 48
- (650) HANZLIK, DE EDS AND TAINTER Arch Int Med, 1925, 36 447
- (651) HANZLIK AND DE LOS J Pharm Exp Therap (Abel Memorial), 1926
- (652) SUNDERMANN Deutsch med Wochnschr, 1924, 50 990
- (653) WESSEL Med Klin, 1924, 20 714
- (654) BEHR Münch med Wochnschr, 1904, 51 1998
- (655) SEIBERT Med Rec, 1911, 79 432
- (656) BRUGSCH Therap d Gegenw, 1905, 46 63
- (657) SANTINI Gazz d Osp, 1904, No 100
- (658) KLOTZ, H S N Y Med J, 1887, Sept 17

## B REFERENCES NOT USED IN THE TEXT

*Salicylic acid and sodium salicylate*

- AULDE Collapse Following Internal Administration of Salicylate of Sodium, Lancet, London, 1890, i, 1299
- BARROWS The Delirium of Salicylic Acid, New York Med Rec, April 29, 1882
- BARTOLI Sopra alcune applicazioni terapeutiche del salicilato di soda, Sperimentale, 1882, 1, 253
- BÉCHAMP Du rôle de quelques acides organiques, notamment de l'acide salicylique et de quelques autres de la série aromatique comparée à celui de la créosote et de l'acide phénique comme antiseptique, Montpellier méd, November, 1875, p 425
- BERNARD, R De l'acide salicylique, Bull de Thérap, 1901, p 141, 565
- BOGGS, A Therapeutic Value of Salicylic Acid, Brit Med Jour, 1878, ii, 558
- BOYLAND Uses of Salicylic Acid, Phila Med and Surg Rep, April 17, 1875, p 301
- BUCH Ueber Salicylsäurelösung als Mundwasser, St Petersburg med Wchnschr, 1878, ii, 96
- BUCHANSKI URCHYNSKI Salicylate in Pneumonia, Russk Vrach, 1913, xi, 1222
- CAIZFREGUES De l'acide salicylique et de son action sur le poulx, Montpellier méd, August, 1877, p 103
- CHAMBERT HÉRON De l'emploi par l'usage externe du sal de méthyle dans la colique hépatique, Gaz med, Paris, 1898, No 34, p 408
- CLOUSTON Salicylate Treatment of Rheumatism, Practitioner, 1882, xxvii, 321 and 401
- DALCHÉ AND COYON De l'emploi du salicyl de soude dans certaines affections hépatiques, Bull gén de thérap, 1899, cxxxiii, 673

- DESPORTES Du meilleur moyen d'administration le salicylat de soude, *Gaz hebdomadaire*, 1884, No 17, p 289
- DIANEUIL Etude sur la médication salicylée, dangers accidents, Thèse de Paris, 1878, iv, 60
- EBSTEIN Zur Kenntnis der Salicylsäurewirkung auf die Respirations Schleimhaut, *Wien klin Wchnschr*, 1896, ix, 187
- EDWARDS Salicylic Acid as Therapeutic Agent, *New York Med Rec*, May 8, 1875, p 329
- FREEMAN Case Illustrating Need of Caution in Using Salicylic Acid, *Lancet*, London, 1886, ii, 1173
- FREUDENBERG Ueber ein neues Arzneivanthem, *Berl klin Wchnschr*, 1878, xlii, 630
- FROHLICH, J Ueber Salophen und dessen therap Verwendung, *Wien med Wchnschr*, 1892, xlii, 1003, 1119
- GASPARINI II solicato sodico nella pleurite, *Gazz med*, 1885, No 11, p 112
- GIBSON Hitherto Unobserved Effect of the Salicylates, *Practitioner*, 1889, xlii, 17
- GLASER Ein Wort für das salicylsäure Natrons, *München med Wchnschr*, 1888, xxii, 365
- GÖTH. Aspirin in der geburtshilflichen und gynakologischen Praxis, *Med Blätter*, 1904, No 6, p 71
- GRABHAM Treatment of Tonsillitis by Salicylate of Sodium, *Practitioner*, 1888, xl, 351
- GRÉLOT De l'usage externe de l'acide salicylique, *Compt rend Soc de biol*, 1877, lxxxv, 93
- GROS Cutaneous Administration of Salicylates in Gout, Rheumatism, and Allied Affections, *Medical Fortnightly*, 1898, xiv, 509
- HAIG, A Influence of Salicylic Acid and Its Salts on the Excretion of Uric Acid, *Med Chr Trans*, 1888, lxxi, 125
- HAYEM Action of Salicylates on Temperature, *Compt rend Soc de Biol*, 1877
- HEFFERMAN A Case of Sodium Salicylate Poisoning, *Brit Med Jour*, 1900, i, 16
- HILLABY The Treatment of Tonsillitis by Salicylate of Sodium, *Practitioner*, 1888, xl, 260
- HUSSON De l'absorption de l'acide salicylique par la peau et des frictions sal dans les affections rhumatismales, Thèse de Nancy, 1896
- HUTINEL Action of Salicylate on Nervous System, *France méd*, 1878
- JOLIN Action of Salicylates on Temperature, *Gaz méd*, 1877
- JONES Poisoning Produced by Thirty Grains of Sodium Salicylate, *Glasgow Med Jour*, January, 1904, p 23
- KÄELIN Ein Fall von schwerer Salicylsäurevergiftung, *Cor-Bibl schweiz Aerzte*, 1896, xxvi, 508
- KEMP On the Use and Abuse of Salicylic Acid, *Brit Med Jour*, 1881, i, 510
- KENNARD. Use of Sodium Salicylate in Treatment of Malarial Fever, *Lancet*, London, 1903, ii, 95
- LESSERE De l'usage interne du sal de methyl pur dans le rhumatisme, *Bull gén de therap*, 1897, cxxxiv, 673
- LUSSANA AND CIOTTO Sul passaggio dell'acido salicilico nel succo gastrico e nell'orina, *Gazz med*, 1877, p 237
- MAMOTI Arch gén de méd, 1879
- MANN Salicylic Intoxication, *New York Med Rec*, Feb 13, 1892, p 181
- MILLER, E L Salicylate of Potassium in Acute Rheumatism, *Therap Gaz*, 1885, ix, 446
- MÜLLER, A W. Ueber die äussere Anwendung der Salicylsäure, *Therap d Gegenw*, 1899, xl, 146

- MÜLLER, P. Neue Salicylpräparate und neue Anwendungsformen der Salicylsäure, Deutsch med Wchnschr, 1904, xxx, 1350
- MUSSY, J. J. L'acide salicylique et le salicylate de soude, Thèse de Paris, 1877, iv, 52
- PAESSLER. Salicyltherapie uod Nephritis bei akuten Gelenksrheumatismus, Therap d Gegenw, 1906, xlvii, 52
- PAGLIANI. Sulla ricerca dell'acido salicilico nelle urine, Arc sc med, 1882, v, 201
- POUCHET. Interpretation de l'action physiologique et thérapeutique de l'acide salicylique, Bull gen de therap, 1896, viii, 65, xvi, 97
- PUTNAM. Salicylates in Acute Rheumatism, Boston Med and Surg Jour, Feb 24, 1876
- RICHARSON. Depressing Effect of Sodium Salicylate, Brit Med Jour, 1897, ii, 1500
- RINGOT. Du traitement du rhéum articulaire par la sal du methyl, Thèse de Lille, 1896
- RUHEMANN. Aspirin und Carcinoma, Deutsch med Wchnschr, 1904, xxx, 849
- SCHUCHARDT. Ueber die Einwirkung der Salicylsäure uod deren Salze auf die Gebärmutter, Thüringer Cor Bl, 1886, No 7
- SCOTT. A Case of Sodium Salicylate Poisoning, Brit Med Jour, 1900, i, 254
- SHARP. Poisoning by Sodium Salicylate, Brit med Jour, 1900, i, 194
- STILLER. Ueber einige Anwendungen des Natrium Salicylicum, Wien med Presse, 1890, xxxi, 6 und 50
- SYLES. Idiosyncrasy to Salicylate of Soda, Brit Med Jour, 1897, i, 972
- THOMSON. Some Evidences of the Action of Salicylates, Lancet, London, 1884, i, 932
- VOELCKER. Limitations to Successful Application of Salicylate Treatment in Rheumatism, Clin Jour, 1911
- WILD. Case of Marked Intolerance of Salicylate of Sodium, Brit Med Jour, 1897, i, 331
- WOODS. Three Cases of Hallucination Due to Administration of Sodium Salicylate, Phila Med and Surg Rep, March 3, 1888, p 273
- YARROW. Salicylate of Sodium in Diabetes Mellitus, Therap Gaz, 1885, ix, 446
- ZAVADSKI. Fate of Salicylic Acid in the Organism, Russk Arch, 1909, viii, 918

### *Salicin*

- BREW. Brit Med Jour, 1876, i, 697
- BROWN. Practitioner, 1877, xix, 209
- CAVAFY. Lancet, London, 1876, ii, 633
- CURNOW. Lancet, London, 1876, ii, 708
- GREEN. Ibid, 1876, ii, 680
- JACOB. Lancet, London, 1876, ii, 254
- MACLAGAN. Ibid, 1876, ii, 601
- MACMILLAN. Ibid, 1876, ii, 729
- NATIER. Practitioner, 1877, xviii, 410
- POLLARD. Brit Med Jour, 1876, ii, 43
- QUI LAN. Brit Med Jour, Dec 6, 1884, p 1124
- RALFE. Lancet, London, 1876, ii, 13, Med Times and Gaz, 1877, No, 13, p 85
- RANCER. Ibid, 1876, ii, 45
- SCHOFIELD. Brit Med Jour, 1876, i, 698
- SENIATOR. Centralbl f med Wissensch, 1876, No 14, p 241 Berl klin Wchnschr, 1877, vi, 181 und 199
- STUART. Practitioner, 1877, xviii, 425
- THOMSON. Brit Med Jour, 1877, i, 509
- TONOLI. Gazz med 1884, pp 353-549
- WALKER. Lancet, London, 1876, i, 729





# THE SIGNIFICANCE OF THE PHYSICAL CONSTITUTION IN MENTAL DISEASE

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## EARLY STUDIES OF BODY TYPES

The question of a connection between external appearance and mental functions has been an ancient preoccupation of the human mind. In following the historical development of this subject, one finds that there enters nearly always into the discussion the preconceived intuitive idea of an essential unity between the morphological

and psychic aspect of the individual. This varies only more or less formally with the development of philosophical ideas concerning the relations of mind and body. It thus happens that until comparatively recent times whenever we look for precise definitions of supposed body types we find psychobiological elements, like physiognomy, general attitude and posture entering into the description, and when we examine descriptions of personality or temperament types we find admixtures of signs taken from humoral pathology, physiology and morphology.<sup>1</sup>

The Hindus (53) (88) distinguished three types of man, called symbolically the hare, the bull, and the horse, and three types of woman, the deer, the mare, and the elephant, supposedly characterized by special qualities of body outline, size of genitals, hair, voice, emotional tendencies, etc. The literature on the doctrine of temperaments, based on Galen's theory of *Krasis*,<sup>2</sup> contains descriptions with a similar mixture of morphological, physiological, and psychological elements, which makes it often difficult, if not impossible, to determine what the various authors meant by their descriptions of temperaments. This holds true also for the nineteenth century medical literature concerning temperaments. The "classical constitutions," the lymphatic, the sanguine, bilious, etc., were still taught in the course on the practice of medicine by Sir Grainger Stewart at Edinburgh in 1890 (58). An extreme and ludicrous example is the distinction of the hemorrhoid and melancholic temperament by Stahl (81), the forerunner of Lavoisier. It is not astonishing, therefore, that the knowledge of morphological body types made very slow progress. The history of racial anthropology affords an analogy where Linnaeus, the first scientist to give man a place in the "natural system," gave a description of four races, *Europaeus albus*, *Americanus rubescens*, *Asiaticus fuscus* and

<sup>1</sup> Compare the derivation of such words as hypochondriacal, phlegmatic, etc., and the traditional body types of dramatic characters such as Henry Percy (Hotspur) and Falstaff in Shakespeare's "Henry IV," Hamlet, the rejuvenated Faust and Mephisto. In order to realize how closely body type and character are interwoven in the eyes of the spectator, one has only to attempt to visualize Hamlet looking like Falstaff, or Falstaff having the physique of Mephisto.

<sup>2</sup> The Greek word *ἁρμῆς* (mixture of body fluids) = *temperies*, the root of the word *temperament*.

*Africanus niger* in which the main characteristics include skin color, body shape, posture and temperament (Scheidt, p 5 (75))

#### BEGINNING OF MEDICAL ANTHROPOMETRIC STUDIES

In medical literature the studies of morphological-physiological types and temperaments, peculiarly intermingled as they were, were from the beginning of scientific medicine influenced by the important consideration of disposition to disease. Hippocrates knew a *habitus phthisicus* and *apoplecticus*. Galen taught that the human constitution (*κατασκευη*), in the Galenic and post-Galenic writings often used synonymously with *habitus* (*εξις*), nature (*φύσις*) and disposition (*διαθεσις*), comes through a disease process (*ταθος*) to a state of disease (*νόσος*) (Gunther, p 2 (28)). It was not until 1860 that Wunderlich, who himself distinguished more physiologically an irritable, strong and limp constitution (Wuth, p 5 (93)), spoke of a promising program for exact analysis and measurement of the physical constitution (Gunther, p 3 (28)). The rise of cellular pathology on the one hand, and bacteriology on the other, prevented for a long time the realization of this program.

The Italian de Giovanni (24) seems to have been the first physician who attempted on a large scale the investigation of physical *habitus* in relation to disease. He fell into the extreme of trying to prove that "the cause of the special morbidity of the organism resides in its special morphology" (p 66). His methods, however, were imperfect, his conclusions very dubious. The historical antagonism between morphological constitutional research and bacteriology is well illustrated in his book, as when he speaks of his reticence toward "the parasitic theories" (p 96-97) and claims that in the human body the *diplococcus* of the saliva can be transformed into the *pneumococcus* and *meningococcus* (p 96). Nevertheless, his researches were both stimulating and suggestive and he became the founder of a productive school of clinical anthropometrists (Viola, etc.). De Giovanni described four morphological types, or "combinations," as he calls them, mainly on the basis of the development of body cavities. These "combinations" (to be discussed later) are, as Bauer (5) states, the prototypes of the body forms described by Kretschmer (44), who has attempted to correlate them with the incidence of definite forms of mental disease.

## ANTHROPOMETRIC STUDIES IN PSYCHIATRY

In psychiatry, just as in general medicine, consideration of the physical constitution is bound up for a long time with the post-Galenic descriptions of "temperaments" in what we now know to be a strange mixture of fancies and facts. It seems interesting that in the very beginning of scientific psychiatry Esquirol (17) compiled statistics regarding the external appearance of his patients. He made the following table (p 157).

Habitudes extérieures du corps	{	embonpoint médiocre	122
		maigreux	60
		obésité	6
Taille <sup>3</sup> . . . . .	{	élevée	102
		petite	19

In the same chapter Esquirol states that generally those patients who are strong and robust (sanguine temperament) tend more to an acute course of the psychosis with more definite crises, whereas others (with a lymphatic temperament) tend to a more chronic and dementing course of the disease<sup>4</sup>. This passage where Esquirol mentions the physical constitution of his mental patients is the more remarkable because it is the only one where Esquirol, whose nosological classification is otherwise purely symptomatic-scholastic, seems to anticipate in a way the modern distinction of affective (manic-depressive) reaction types with acute, attack-like course and schizophrenic reaction types with more chronic and often deteriorating development<sup>5</sup>.

The modern scientific morphological studies in general medicine, undertaken with the view of finding correlations with definite systemic diseases (de Giovanni) were suppressed by the sensational success of

<sup>3</sup> La taille (French) = body height = stature (anthropological terminology)

<sup>4</sup> Compare also Pritchard (70) "It has been observed by M. Esquirol, that when persons of the lymphatic or phlegmatic temperament, or those who have a pale exanguious constitution, fall into mania or monomania, their disorder is more liable than that which occurs in other constitutions to pass into dementia or incoherence."

<sup>5</sup> It may be noted as a digression that Esquirol also knew the occurrence of cyanosis in hands and feet of schizophrenic patients. In the good description of a case under the diagnostic heading of "melancholia," which leaves no doubt that the case is one of what we would now call schizophrenia, he says "Ses mains sont souvent violettes ainsi que ses pieds."

cellular pathology and bacteriology. They were revived only with the rise of modern endocrinology. This renewed interest in morphology was based on the observation that, due to certain endocrine disorders, individuals show morphological changes and that these individuals, as for example in cretinism and acromegaly, tend to lose their racial and family resemblance, but show a morphological similarity among each other (Wuth (93), p. 1-2). These endocrinological studies were fruitful in certain definitely pathological cases. In regard to morphological (and psychological) types they have yielded very little that may be regarded as definitely established.

The investigation of the physical constitution in psychiatry was deflected in a different direction. Influenced by Gall, though opposed to his doctrines, Morel (61) propounded his theory of degeneration which has influenced psychiatric thought profoundly until the present day. Physical signs of degeneration were the basis of Morel's ideas, he found it necessary in order to understand degeneration to study the "natural history of man." His knowledge of physical signs of degeneration, however, was scanty. He laid particular stress on the variations in the human ear, of which he described one form, the so called Morel ear. On this subject sprang up a whole special literature in psychiatry. In his later work, "*Traité des maladies mentales*," Paris, 1860, where he stresses again and again bodily degeneration as the basis of hereditary mental disease, he devoted only five of 860 pages to the description of physical signs of degeneration. The reticence of Morel is in contrast to the enormous expansion of the doctrine of morphological degeneration signs by Lombroso, who studied morphological anomalies primarily from the point of view of criminology. Both Lombroso's anthropological and statistical methods were uncritical. Many of his results were disproved when more exact methods were employed. Little today remains valid of Lombroso's life work, and whatever is left of the physical signs of degeneration, the stigmata hereditatis as Morel called them, belongs to the sphere of constitutional variations and diseases. Theoretically these physical signs of degeneration, as they are wrongly called, are of great interest. Their study with regard to etiology and correlation with other morphological signs is by no means completed. Figure 1 shows an example of a morphological characteristic which has been regarded as

environmentally determined, but which is really constitutional, namely the atrophy of the fifth toe in man. Schultz (79) describes a morphological variation which might easily be mistaken for a constitutional racial stigma but which he proved to be environmentally deter-

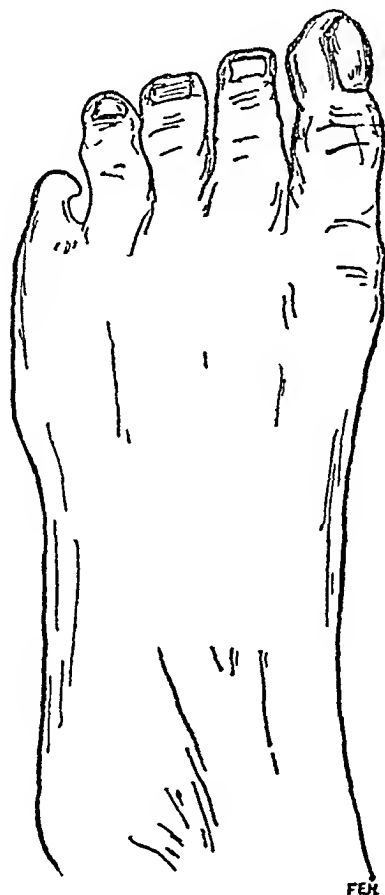


FIG 1 FOOT OF AN EGYPTIAN MUMMY OF THE XI DYNASTY—ABOUT 1300 B C—CENTURIES BEFORE BOOTS APPEARED IN EGYPT

The last phalanx is diminutive, and its joint is ankylosed. From photo by Dr George Sobhy, Cairo, in *Journal of Heredity*, 1917

mined, namely the peculiar position of the fifth finger of the Rama Indian (see fig 2). Lombroso's interpretation of "physical signs of degeneration," namely, his theory of anatomical-biological regression in born criminals to the morphological status of lower races, prehistoric man and animals (Lombroso's follower, Kurella, spoke of

primatoid skull forms) had to be largely given up Sommer (quoted by Fischer (19)), who to some extent has recognized Lombroso's teachings, has pointed out that Lombroso has confused two separate problems first, the problem of whether the *delinquente nato* really exists, secondly, if he does exist whether this abnormality is characterized by significant morphological features Just as Lombroso's methods were challenged there was also a strong criticism of the uncertainty in the definition of his object of study, namely what really constituted a born criminal There is a certain analogy between the formulation of this

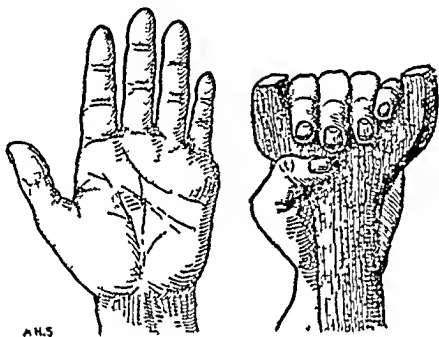


FIG 2 SKETCH OF HAND OF A RAMA INDIAN AND OF THE MANNER IN WHICH THE HANDLE OF A NICARAGUAN PADDLE IS GRIPPED

Note the position of the little finger This drawing shows a morphological variation easily mistaken for a constitutional racial stigma — After Schultz (79)

problem and the problem which at the end of the 19th century confronted physical anthropologists who used exact anthropometric measurements in psychiatry Having successfully studied and differentiated ethnic groups with modern methods, anthropologists attempted to distinguish with anthropometric methods the "insane" from the "normal" individuals In an excellent paper, which from the point of view of anthropometric methods is in many ways as useful today as it was then, Hrdlička (35) formulated a program "The new program is, after being able to define the human normal, to separate the abnormal from the normal, and to classify, if possible, the ab



normal And it is here, in this its latest application, where anthropology encounters the domain of medicine As an aid in determining the abnormal in man, it serves both the general student of mankind and the clinician, and they really join hands at this point, the anthropologist and the physician" (p 523) It is, however, exceedingly difficult in psychopathology to make a generic distinction between abnormal and normal With the closer dynamic study of psychopathological conditions it became more and more apparent and may be regarded as well established today that elements of certain psychopathological reactions reach far into the sphere of psychopathic personalities (that is to say, of people who though constitutionally slightly abnormal may not suffer from a circumscribed mental disease) and even far into the group of normal people This is true also for the two large and most common psychopathological reaction types, the manic-depressive and the schizophrenic It is, therefore, not astonishing that generally valid significant morphological correlations with "normals" and "abnormals"<sup>6</sup> were not found, and that on the other hand, with the clarifying of our psychiatric diagnostic conceptions, contrasts between two mental diseases offer a better object of study for anthropological correlations

Modern heredity studies in psychiatry have gone through an analogous development The pioneer researches of Koller and Diem have shown that there are no very significant differences as regards the quantitative incidence of mental disease in the ancestry of "normal" and "abnormal" individuals The tendency of modern heredity studies in psychiatry has been more and more to draw on all even slightly abnormal relatives and finally on all members of the family (see Kahn, p 48 (38)) Despite the progress of modern hereditobiological research in psychiatry, the knowledge of even a complete family history does not give a clue to the pathogenetic factors of psychoses For this study the modern dynamic and analytic point of view proved more fruitful, and, inasmuch as it emphasizes changeable

<sup>6</sup> The impasse which is easily reached by making the distinction "normal" and "abnormal"—that is to say a "monotype standard"—the starting point of investigations, is of course not confined to psychiatry alone The early X-ray studies of the stomach where all sorts of atonic conditions were described on the basis of a preconceived normal one-type standard are an example This subject is well discussed by Mills (59)

psychogenic and environmental factors, more practically and therapeutically useful

### HEREDITY AND CONSTITUTION

However great the advances in the knowledge of exogenic etiological factors of disease have been in the various stages of medical progress, the age-old and unavoidable experience both in general medicine and psychiatry, that different individuals react differently to similar kinds of exposure, has always prevented the suppression of the recognition of hereditary factors of disease, from the "res naturales" of the old physicians to the "constitutional factors" of modern pathologists. The term constitution is used by different pathologists in a very different and arbitrary way. Without going into detail in the examination of these different definitions it seems correct to say, that most of these formulations are more logically precise than practically directly applicable according to our present state of knowledge. It is not yet possible in human pathology always to distinguish with exactness between hereditary (often used synonymously with unchangeable) and acquired signs. We are forced to assume that the Mendelian laws of heredity apply also to anthropology in the widest sense (Eugen Fischer (18), p. 136). In fact it has been claimed that the only binding proof of the hereditary character of any sign, is the knowledge of its mode of transmission according to the Mendelian laws (Fischer, loc. cit., p. 137). In the human organism, however, the delimitation of "hereditary units" is infinitely more complicated than in plants. Bornhardt (9) comes to the conclusion that it is not possible to divide constitutional anomalies into hereditary and acquired. The concept of constitution cannot have a heredo-biological foundation alone. He therefore also disagrees with Tandler's distinction between constitution and condition. If the difficulty of distinguishing between hereditary and acquired traits be true in the sphere of human morphology, it is self-evident in the sphere of psychobiological integration. The formulation of constitution as disposition to disease, as a measure for the resistance of the organism toward pathogenic influences (Martius, Strümpell) is too narrow, since disposition to disease is only one correlated sign or a correlated combination of signs among many others (Lewin (32) p. 103). To confine constitution to morphology alone

TABLE 1  
*Classifications of body types*

	1	2	3	3a	4
Hippocrates Walker (1852)	Locomotive beauty (Diana)	Habitus apoplecticus Nutritive beauty (Venus)	Habitus phthisicus	Mental beauty (Mincerva)	
Carus (1853)	Athletic, lascivious, plethoric arterial constitutions (bones and mus- cles strongly devel- oped)	Phlegmatic, bocotic, plethoric venous, choleric, apathic constitutions (re- gion of digestive organs prominent)	Asthenic, sensory, pneumatic, chloro- tic, phthisic, lym- phatic constitu- tions (narrow chest, long body, skele- ton and muscles poorly developed)	Cerebral constitu- tion (delicate)	Sterile, atrophic con- stitutions (general and special sex characteristics little developed)
Rokitsky- Beneke	Normal type, dis- position to uncon- stitutional diseases only	Types with disposi- tion to carcinoma, hyperplastic	Types with disposi- tion to tubercu- losis, hypoplastic		
Kundrat					Primary vegetation disorders (hypo- plasias, etc.)
De Giovanni	Second combination, plethoric	Third combination	First combination, phthisic		
Manouvrier	Mesoskèles	Brachyskèles (mikroskèles)	Makroskèles		
Viola	Normosplanchnic type	Brevignes Megalosplanchnic type	Longignes Microsplanchnic type		

Femur	Hypervertigative biotype	Hypovertigative biotype	Cerebral type	Primate anomalies (similarities to primates)
Simand	Muscular type	Digestive type	Respiratory type	Dysplastic types
Bryant	Herbivorous type	Ilypotonic	Carnivorous type	
Tandler	Hypertonic		Asthenic habitus	
Bauer	Sthenic	Arthritic habitus	Hyposthenic, asthenic	
Mills		Hyposthenic	Narrow chested	
Brugsch	Normal chested	Wide chested	Asthenic type	
Kretschmer	Athletic type	Pyloric type	Slender biotype	
Davenport	Medium	Fleshy	Hyperostomorph	
Bern	Normal	Mesomorph	Linear type	
Stockard		Lateral type	Slender	
Aschner		Broad		

(Hering (32)), is not practical and an unnecessary restriction Without venturing to give a definition which would be theoretically binding, one may therefore, for the purpose of investigations like these, speak of the human constitution as the correlative unity of those morphological, physiological and psychobiological developments of the individual which are definitely more influenced by heredity than by environment.

#### COMPARISON OF CLASSIFICATIONS OF MORPHOLOGICAL TYPES

Attempts to describe morphological constitutional types have been made very frequently None of these classifications, however, obtained final recognition (Wuth, 1 c, p 5) In many the very nomenclature shows the influence of physiognomical-symbolical ideas Table 1 gives a cursory schematic survey of the various classifications of body types <sup>7</sup>

Such a comparison of type constructions may give rise to the serious and not unjustified objection that these types originated at different ages and through totally heterogeneous methods, scientific and fanciful Moreover it may appear inappropriate, or even unjust, to chart side by side the classical traditional types of Hippocrates, the romantic-symbolic system of Carus, the esthetic mythological analogies of the English anthropologist Walker, the dogmatic pathological "combinations" of de Giovanni, and the clinical anthropometric findings of Manouvrier, Viola, Brugsch, and Davenport, the brilliant intuitive divisions of Sigaud and his pupils which have been put to clinical use by Julius Bauer (5, 6), the pathological-anatomical observations of Rokitanski, Beneke and Kundrat, the anatomical types of Mills and Stockard, and the careful clinical descriptions of the psychiatrist Kretschmer Nevertheless, it seemed worth while to collect and tabulate this not easily accessible material, because it seemed to illustrate several important considerations

<sup>7</sup> Compiled from Aschner (2), Bauer (5), Bean (7), Brugsch (11), Bryant (12), Carus (13), Davenport (15), Dubreuil-Chambardel (16), de Giovanni (24), Hallé et Thillaye (29a), Kern (40), Kretschmer (44), Kundrat (48), Manouvrier (54), Mills (59), Pende (65), Rostan (73a), Stockard (85), Stratz (90) A number of these publications contain good illustrations The illustrations show in many instances an unmistakable similarity between the types described by different authors The photographs in the paper by Mills (1917) can be especially recommended The photographs given by Bach (3) showing the comparison between the typical pyknic habitus and the physique of a professional wrestler are instructive

The influence of physiognomical-symbolical notions and of clinical pathological observations, expressed in the nomenclature itself again and again, is striking, especially if it is taken into account that many of the authors did not know about one another. One of the fundamental mistakes of some of these classifications Kretschmer (44) has expressed very clearly, speaking of the types of Sigaud and his pupils

"their occasionally correct observations of detail are forced into a scheme which has been constructed purely speculatively, and at the basis of which—if we may express ourselves somewhat naïvely for the sake of clarity—lie the following ideas: there are (1) men of reason—these must have a big head, (2) eaters, these must have a fine belly, (3) acrobats, these must have splendid muscles, and (4) runners, these must have a fine pair of lungs" (p. 17)

The various types given in the groupings of different authors do not, of course, correspond with each other in the simple fashion schematically indicated on the chart. The question arises as to what extent they are comparable. There is no doubt that there is a thread of uniformity and that in a far-reaching way most of these classifications aim to express similar body forms. A few are almost identical. It is difficult to determine how close this correspondence is between the groupings of different authors, but the difficulty seems almost equally great when the attempt is made, with any amount of accuracy, to assign an individual to any one type of these morphological classifications.

#### OBSERVATIONAL AND ANTHROPOMETRIC METHODS IN GENERAL

With regard to methods the problem arises, whether in the systematic differentiation of recurrent forms of habitus of individuals one should rely on exact anthropometric measurements alone, on descriptions alone, or on a combination of both. This problem has a parallel in the history of racial anthropology. The extreme number of anthropometric measurements used by the Hungarian Toró, who took five thousand measurements of the skull alone, was opposed by Sergi who proposed at one time to omit measurements altogether and rely on observations alone (Haddon (29), pp. 10-41). Experience with patients seems to indicate that the question is not such a simple one of either the one or the other or both. Even when a decision is made that inclusion of measurements in the working scheme is necessary

there still remains the greater problem of the choice of measurements to be used. This problem is not simplified by the fact that since investigations of this character are of a clinical rather than an anthropological nature, they must in all respects be adapted to the needs of the clinic.<sup>8</sup>

It is evidently possible to recognize recurring (i.e., typical) body forms from observations alone. The process of this recognition is a complicated one, an exact observation of certain details combined with the realization of the general impression of the individual in toto. In these observations the personal equation plays a not insignificant part. Undoubtedly this general unison impression is very useful and important, and requires training and technique.<sup>9</sup>

This procedure of judgment from observations has been very much criticized. Unfortunately the average medical clinician is not qualified to raise the objection that it is impossible to size up recurrent body types from general impression because as a rule he does not, during the examination of a patient, inspect the nude human body in an erect posture and at an appropriate distance. This is the only way to get a clear impression of the general body configuration type. The reason why the general practitioner as a rule does not do this is two-fold. First, there are obvious practical obstacles with regard to the routine technique of medical examination. Secondly, clinicians are interested mostly in disturbances of body structure when there are more or less pronounced anomalies, as in pathological-endocrine types.

It is a different matter, however, to describe and recognize again more or less accurately certain body types and to prove their existence inductively, study their occurrence statistically and establish quantitative relations with other correlative signs such as the incidence of disease. Racial anthropology is confronted with similar but by no means identical problems. Races are distinguished by observational data, such as color of hair and skin, quantity of hair, shape of head and by anthropometric data relative to body proportions. Just those data

<sup>8</sup> We are greatly indebted to Dr. Adolph H. Schultz, Associate Professor of Physical Anthropology, Johns Hopkins University, for his never failing encouragement, advice and critique throughout the course of this study.

<sup>9</sup> We found it useful in the process of training ourselves to compare our observations reached independently and to discuss the discrepancies.

which are most useful in racial anthropology, however, namely complexion, form of hair, skull form, eye color and stature, are apparently of least importance in the differentiation of smaller non-racial groups of individuals such as groups afflicted with physical or mental disease.<sup>10</sup> For this purpose the study of the body proportions, and particularly the development of the body cavities, as de Giovanni has already recognized, is of first importance.

In psychiatry the morphology of the skull has often been regarded as of very particular significance. This primitive-symbolic belief that the morphology of one single part of the human body, quite apart from the rest of the body, must have an exceptional value as an indicator of mental faculties,<sup>11</sup> has probably also something to do with the age-old observation that microcephaly is not infrequently associated with idiocy. That the opposite is not true, namely that a large head does not denote a superior intelligence or yet a deficient one, was already known to Perdulcis (66), who states this explicitly.<sup>12</sup> There are only two points which give the morphology of the skull an exceptional position. One is the undoubted fact that there is a certain inter-relation between the development of the brain and the cranium. The scientifically well-established facts concerning this inter-relation are, however, very few. Reichardt's (73) finding of relatively small skull cavity and relatively high specific gravity of the cranium in schizophrenic, especially catatonic patients, is interesting and significant. The other point is that the formation of the skull may be,

<sup>10</sup> It is for considerations like these that the expression "disease races" used by Dr. G. W. Draper of New York seems unfortunate.

<sup>11</sup> Compare the head formation in statues of the Buddha. "It will also be noticed that the Buddha images have certain physical peculiarities of which the most conspicuous is the ushnisha or protuberance on the top of the skull. Technically this appears to be derived from a western form of headdress, but in significance it is to be classed with the physical characters attributed by Indian physiognomists to the Superman, the Mahapurusha. This ushnisha serves to distinguish the Buddha figure from that of a mere Brother, for the head of the Bhikkhu is always shaved bare and without the Buddha's bump of wisdom" (Coomaraswamy (14), p. 331). The ushnisha does not grow only as an attribute of the Buddha with his growing wisdom and after his illumination but is already present as a "constitutional sign" in all statues depicting Buddha as a child. See Adam (1) "Buddha as a child," plate 13.

<sup>12</sup> "Alioquin magnitudo capitis ut non bonam, sic non semper malam per se constitutionem indicat" (p. 62).



to some extent, an indicator of the formation of the rest of the body especially of the skeletal system, as was already known to Hippocrates. The teaching of Gall<sup>13</sup> has left behind it the belief that whatever correlation there may be between morphological and psychological traits must be expressed particularly clearly in the form of the skull. Peterson (67) regretted that we have no studies of the psychic histories of tribes who produced artificial malformation of their heads. It seems also significant in this connection that the mental reactions of otherwise crippled children and adults have received very little attention on the part of psychiatrists. De Giovanni and Viola were the first to prove that head and skull measurements can be neglected to some extent in constitutional researches. Borchardt (10) in a recent study agrees with this view.

Some authors, like Kretschmer (43), claim that description goes very much further than measurements, and that description alone is entirely sufficient to differentiate types. From anthropometric measurements he expects only a more exact formulation. He has supplemented his book with a comparison of the averages of absolute measurements,<sup>14</sup> a procedure anthropologically of little value. Mayer-Gross (57) has gone even further and believes that the study of morphological types in psychiatry should be independent of the exact methods of physical anthropology, and more a branch of psychology which can be compared with the study of other expressive phenomena like "graphology." This lack of distinction between physiognomic expression and mensurable morphology reminds one of the old temperament theories. Scheidt (76), on the other hand, emphasizes that these studies can have conclusive results only if they make use of the commonly accepted methods of physical anthropology, the uniformity

<sup>13</sup> It is not intended here to discuss the historical significance of Gall's teaching. That Gall's influence was not entirely a side-tracking one for neuropsychiatric research can be seen from the fact that one of the first cases of aphasia with an autopsy report of a lesion in the left frontal region of the brain was published by Thomas Hood in the "Phrenological Transactions," a journal devoted to Gall's teaching (Walter (91)).

<sup>14</sup> In physical anthropology absolute measurements such as head length or leg length are used as well as indices. An index expresses the percental relationship between two or more measurements. For example, the cephalic index =  $\left( \frac{\text{breadth}}{\text{length}} \times 100 \right)$ . Index values are generally regarded as more significant than absolute values.

of which has been established more or less successfully at international congresses of physical anthropology (Compare also Hrdlička Anthropometry (34)) It is true that every new problem is apt to call for certain adaptations and alterations in technique, but the same principles should be followed

The task of an investigation of morphological and psychopathological correlations<sup>15</sup> therefore resolves itself into the following questions can recurrent typical body forms be determined by inductive anthropometric methods, can body types, differentiated by observation and description, be correlated with exact anthropometric data, are there any correlations between anthropometric and psychopathological findings?

#### THE MATERIAL OF THIS STUDY, PROCEDURE OF INVESTIGATION

The material of this study consists of sixty-five male patients chosen at random without any consideration of diagnosis or physical habitus The patients were taken from the wards of the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, and from the Spring Grove State Hospital, Catonsville, Maryland <sup>16</sup> A series of thirty-one female patients who were observed and measured at the same time<sup>17</sup> is omitted from this study for the following reasons anthropological data from female individuals are not strictly comparable with those of male individuals, dimensional changes of habitus at different ages are more marked in women than in men (Aschner (2), p 125), the physical types described by Viola, Sigaud, and Kretschmer are more difficult to recognize in women (Bauer (6) mentions this for Sigaud's types, p 1082), in very many anthropological studies women are omitted It seemed that if there are significant differences in morphological habitus between individuals with different mental diseases, as Kretschmer has claimed, these differences should be at least indicated in an accurate study of a relatively small number Since our material is diagnostically entirely unselected (except that the routine procedure of the Henry

<sup>15</sup> By "correlation" is understood "a more frequent concurrence of two phenomena than would be expected from a mere chance coordination" (Scheidt (75))

<sup>16</sup> We acknowledge gratefully the cooperation of Dr J Percy Wade, Superintendent, Spring Grove State Hospital

<sup>17</sup> A study of these female patients is in progress

TABLE 2

NUMBER	NAME	DIAGNOSIS	PRE-PSYCHOTIC PERSONALITY	BODY TYPE	INDEX
Predominantly affective reaction types					
1	E L	Hypochondriacal depression in intellectually debile person	Syntropic	Pyknoid	237
2	W P	Depression with unreality feelings following acute anxiety state		Pyknoid (athletic)	247
3	D W	Manic-depressive reaction type, depressive phase	Syntropic	Pyknoid (athletic)	302
4	M C	Depressive personality with circumscribed aggravations		Pyknic	212
5	R R	Agitated depression—third attack		Pyknoid	224
6	L M	Manic-depressive reaction type, depressive phase		Pyknic	182
7	G N	Mania, previous attack of chronic mania		Pyknic	206
8	J H	Manic-depressive reaction type, manic phase with schizophrenic elements (periods of inaccessibility, mutism, day dreaming and catalepsy), previous depressive attack	Syntropic	Asthenic (dysplastic features)	325
9	D K.	Psychoneurotic depression—third attack			
10	B R	Manic-depressive reaction type, fourth depressive attack		Pyknoid (athletic)	296
11	H G	Manic-depressive reaction type, hypomanic state Previous manic-depressive cycles		Pyknic	154
				Unclear	315
12	H A	Reactive depression with protracted fatigue symptoms	Syntropic	Pyknoid (athletic)	255
13	R M	Manic-depressive reaction type, depressive phase		Athletic	266
14	H D	Depression with somatic delusions, previous psychotic attack at fourteen		Unclear	257
15	T D	Agitated depression, second attack, cerebral arteriosclerosis	Syntropic	Pyknoid	262
16	W F	Manic-depressive reaction type, second depressive attack		Pyknic	167
17	T B	Manic-depressive reaction type, depressive phase Previous manic-depressive cycles		Pyknoid (athletic)	276
18	E F	Depression with schizophrenic elements (auditory and visual hallucinatory experiences and ideas of reference)	Syntropic	Asthenic	291

19	M J	Manic excitement with schizophrenic elements (feelings of influence, revelation experiences, hallucinations of Cod's voice through canary bird)	Predominantly schizophrenic reaction types	Asthemic athletic M Γ	126
20	N S	Schizophrenic reaction type	Idiotropic	Asthemic (dysplastic features)	313
21	H T	Schizophrenic paranoid reaction type	Idiotropic	Asthemic athletic M-Γ	299
22	W S	Schizophrenic paranoid reaction type	Idiotropic	Asthemic	306
23	B S	Catatonic stupor	Idiotropic	Asthemic athletic M Γ	314
24	C K	Anxiety state with schizophrenic paranoid development	Idiotropic	Pyknoic (athletic)	199
25	J H L	Schizophrenic paranoid reaction type	Idiotropic	Asthemic athletic M Γ	292
26	R C	Schizophrenic reaction type	Idiotropic	Unclear	267
27	J C	Schizophrenic paranoid reaction type with early catatonic phase	Idiotropic	Asthemic (dysplastic features)	298
28	H B	Schizophrenia—simple type	Idiotropic	Asthemic (dysplastic features)	337
29	M B	Schizophrenic paranoid reaction type	Idiotropic	Asthemic	248
30	T W	Schizophrenic reaction type	Idiotropic	Asthemic athletic M Γ (dysplastic features)	270
31	G G	Schizophrenic paranoid reaction type	Idiotropic	Asthemic (dysplastic features)	315
32	J H	Schizophrenic reaction type	Idiotropic	Asthemic athletic M Γ	252
33	G W	Schizophrenic paranoid reaction type	Idiotropic	Asthemic	268
34	H O	Schizophrenic reaction type	Idiotropic	Asthemic athletic M Γ	260
35	A B	Schizophrenic reaction type	Idiotropic	Asthemic	301
36	F S	Schizophrenic paranoid reaction type	Idiotropic	Asthemic athletic M Γ (dysplastic features)	333
37	C I	Schizophrenic reaction type, scattered deterioration	Idiotropic	Pyknoic (asthenic)	242
38	G A	Schizophrenic reaction type, scattered deterioration	Idiotropic	Asthemic (dysplastic features)	282
39	A G	Schizophrenic reaction type	Idiotropic	Pyknoic (athletic)	294
40	W B	Schizophrenic reaction type	Idiotropic	Pyknoic (athletic)	229
41	J H	Schizophrenic reaction type	Idiotropic	Pyknoic (dysplastic features)	178

NUMBER	NAME	DIAGNOSIS	PRE-PSYCHOTIC PERSONALITY	BODY TYPE	INDI X
Predominantly schizophrenic reaction types—Continued					
42	A B	Schizophrenic reaction type, social recovery	Idiotropic Idiotropic	Athletic	263
43	R D	Schizophrenia—simple type		Asthenic-athletic M-F	302
44	M S.	Schizophrenic reaction type		Athletic (dysplastic features)	254
Psychopathic personalities + psychoneuroses					
45	R. O.	Psychopathic personality, alcoholic hallucinosis	Idiotropic	Asthenic-athletic M-F	284
46	B R	Chronic alcoholism		Athletic	299
47	J G	Intellectual debility, hysteria		Pyknoic (asthenic)	271
48	W B	Constitutional psychopathic inferiority, emotional instability		Asthenic-athletic M-F	311
49	J H.	Post-traumatic hypochondriasis	Syntropic	Pyknic	224
50	F W	Supra-orbital pain on psychogenic basis		Pyknoic	243
51	J M	Feeble-mindedness		Asthenic-athletic M-F	296
52	W N.	Constitutional psychopathic inferiority, emotional instability, alcoholism		Asthenic-athletic M-F	282
53	L. S	Atypical tabes (?), hysterical reaction	Syntropic	Pyknic	153
54	J A	Feeble-mindedness with schizophrenic-like psychotic episodes		Pyknic	197
55	R W	Constitutional psychopathic inferiority, antisocial tendencies		Pyknoic (athletic)	242
Organic reaction types					
56	C P	Epilepsy	Syntropic  Syntropic	Asthenic	298
57	C D	Dementia Paralytica		Pyknoic (athletic)	227
58	F S	Dementia Paralytica with previous depressive attack		Pyknoic (dysplastic features)	234
59	C A	Cerebral lues		Pyknic	214
60	C C	Epilepsy		Pyknic	186
61	J R	Epilepsy		Pyknoic (athletic)	243
62	G I	Metencephalic Parkinson syndrome		Pyknic	199
63	A S	Dementia paralytica		Pyknic	194
64	L B	Depressive psychosis following encephalitis lethargica		Asthenic-athletic M-F	276
65	G A	Left hemiplegia		Asthenic-athletic M-F	304

Phupps Psychiatric Clinic prefers early and diagnostically complicated or therapeutically promising cases, and the material from the State Hospital naturally tends to a predominance of chronic cases), a variety of diagnostic groups is represented. Kretschmer's book and the studies of most investigators based on his book deal only with manic-depressive and schizophrenic cases.

The patients are classified in four diagnostic groups

- 1 Predominantly affective (manic-depressive) reaction types
- 2 Predominantly schizophrenic reaction types
- 3 Organic reaction types
- 4 Psychopathic personalities and psychoneuroses

This division was made purely for practical purposes in order to avoid a larger number of diagnostic groups with only a few individuals in each group.

In the first group are placed nineteen cases of affective psychoses,<sup>18</sup> both cases with more or less typical course of manic-depressive psychosis and cases which, though predominantly affective, present certain other features such as schizophrenic-like reactions. The special diagnosis of each case is given in table 2. In the same way there are in the second group twenty-five predominantly schizophrenic patients with the special diagnosis indicated. In the third group are eleven cases of psychopathic personalities and psychoneuroses, including also cases of chronic alcoholism, a diagnostically not quite clear case of post-traumatic hypochondriasis, and, merely for the practical considerations mentioned above, cases of feeble-mindedness. In the fourth group are ten cases of organic reaction type including epilepsy.

The nosologically indefinite arrangement of cases in the last two groups is of little significance inasmuch as the emphasis of the study is naturally on the two more constitutional reaction types of the first two groups. In these first two groups it seemed of special interest to see whether those cases for the sake of which the qualification "predominantly" was introduced showed any special features. The designation of manic-depressive psychosis with

<sup>18</sup> This term is used in a similar meaning by Kahn in a recent study (37).

phrenic features is not intended to indicate a co-existence or blending of different "hereditary units," but is employed merely in order to do justice to the clinical facts of the individual case. It may be added that more or less typical manic-depressive reaction types according to any strict terminology are relatively rare in hospitals, as compared with schizophrenic psychoses, so that serious doubt has been cast on the diagnostic conscientiousness of those investigators who have studied in a relatively short time the same large number of manic-depressive and schizophrenic psychoses (Kolle (42), p. 605).

In the course of the investigation three kinds of data were kept entirely separate, namely,

- 1 Psychiatric data
- 2 Data obtained in form of observations
- 3 Anthropometric data

Each set of data for each patient was separately numbered, and the psychiatric, observational, and anthropometric data not compared until the final correlation. The formulation of the psychiatric diagnosis was written down in the present form (see table 2) before the anthropometric valuations were completed.

#### DESCRIPTION OF MORPHOLOGICAL TYPES USED

In the classification of morphological types we followed mainly the descriptions given by Kretschmer (44). From the observation of our patients and from exact anthropometric data (to be discussed later) a group of patients seemed to be distinct enough to be classed together as a sub-type or transition type which we shall refer to as pyknoid. The chief characteristics of these types are as follows:

1 The pyknic individual (plate 1) has in profile a round head, the contour of the occiput, top of the skull and profile line impressing one often as a more or less clear circle. The outline of the head is soft without any sharply prominent parts (like nose or chin). The face has the form of a pentagon or a shield (see fig. 3, I and II) or in many cases a form between the two. It is always definitely broad and soft, quite apart from the fact that it is usually fleshy, especially as regards the nose. There can be no doubt that in the general aspect of the

face the impression of a certain harmoniousness and balance is also conveyed by certain physiognomical psychological characteristics which evidently may be a source of error. The neck is short and full, with the head set a little forward on smoothly rounded shoulders. The line from the tip of the chin to the suprasternal notch is characteristic, inasmuch as it tends to be not an angle but a smoothly sloping or even a straight line<sup>19</sup>. The hair line usually borders the forehead in a regular unindented curve. Apparently the pyknic type has a tendency to baldness, and when this occurs it seems to be electively regular in outline and with a smooth shiny surface. The trunk is thick set and appears barrel-shaped, with the chest broadening

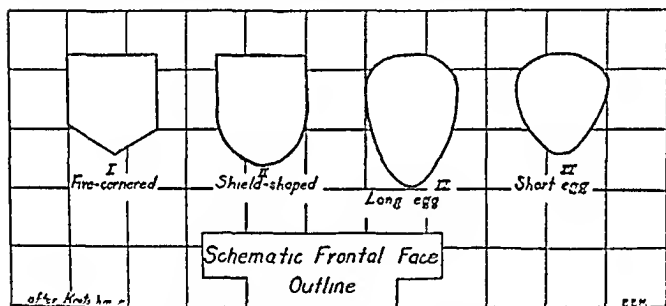


FIG. 3. SCHEMATIC REPRESENTATION OF THE FACIAL OUTLINE

toward the lower part of the body. One might say that the body cavities (head, chest, abdomen) tend to a voluminous development. The limbs are relatively short, as are also the hands. The panniculus adiposus is well developed and the color of the skin is good. The pyknic habitus is most definitely pronounced in early middle age.

1a. There are undoubtedly pyknic admixtures in other cases and in order to do justice to these frequent not so distinct types which

<sup>19</sup> The passage in Kretschmer's book (English translation), p. 29 (44), where this trait is described has been wrongly translated so that the meaning has been destroyed. The translator evidently confounded the German word "Sternalende" which means end of the sternum, with the word "Stirne," meaning forehead. This passage has been quoted uncorrected in a number of reviews of the subject.



impress one as having definitely pyknic components we propose to speak of a pyknoid habitus

2 The athletic type is characterized by a strong development of the locomotor apparatus so that the bones and muscles stand out in plastic relief. The heavy development of the skeleton is most easily recognized in the clavicles. The neck is strong and the trapezius muscles typically very well developed. The shoulders are large and the trunk tapers down from the broad shoulder girdle to the relatively narrow pelvis, so that the trunk outline from the front can be schematically designated as a trapezoid<sup>20</sup>. The limbs are relatively long, the hands and feet are large and the fingers often of a blunt, thick and "acromegaloid" character. The hair is abundant and the hair line tends to grow in a peak in the center of the forehead, receding in bay-like manner on either side toward the temples. The face has a long egg<sup>21</sup> form (see fig 3, III). A line which would connect the upper forehead, tip of nose, and chin would be a gentle curve. There is a variant, if one may speak of such, which is on the whole more plump and massive.

3 The asthenic habitus<sup>22</sup> (plate 2) is characterized by the general impression of a deficiency in volume combined with an average un-lessened length, so that these individuals impress one as being taller than they really are. The thorax is long and flat and the shoulders narrow, and the trunk can be schematically described as cylindrical. The legs and arms are long and thin with lean muscles. The face is of short egg form (see fig 3, IV) and may show hypoplasia in varying degree. The skin tends to be pale, thin, and with but scant fat. The profile is usually markedly irregular. The line which would connect upper forehead, tip of nose and chin tends to be angular on account of the disproportion between the long nose (which seems sharp on account of lack of fatty upholstering) and the small mandible. When the hypoplasia of the jaw is not so marked there may be noted simply a long nosed profile. The neck is thin and seems elongated. The

<sup>20</sup> The Hindus compared this type of trunk with the head of a cow (Tagore (87))

<sup>21</sup> The Hindus compared a type of face with the egg of a chicken (see Tagore (87), p. 24)

<sup>22</sup> This term is used here not in a clinical but in a purely morphological sense. Stiller (84) described a "morbus asthenicus" in which he included almost all deviations from the normal constitution. Compare also Zerner (94)

body hair is scanty and these individuals may also tend to baldness, but with an irregular outline and a more or less wrinkled surface. Other individuals who on account of some signs might be subsumed under this type have wider shoulders accompanying the usual flat chest.

4. Dysplastic body forms show stunted growth either of the whole body or parts, i.e., very small nose or minute hands and feet or dysgenital (eunuchoid) features (long extremities, broad pelvis, scanty hair, unusual distribution of fat). The undergrowth of the nose, together with a certain softness of the facial outline, may give the face a pseudo-pyknice appearance, as can also eunuchoid obesity of the trunk. However, this habitus can be easily distinguished from the pyknic type by attention to details. On account of the underdevelopment of the middle part of the face the line connecting upper forehead, tip of nose and chin may approach a straight line. On the whole this group of individuals with dysplastic features contains all the very marked variations from the most common types.

#### METHODS OF OBSERVATION AND DESCRIPTION

The following observations were recorded for each patient <sup>22</sup>

- |  |  |
|--|--|
| 1 Fractures                                    | 16 Musculature   |
| 2 Right handed                                 | 17 Scapulae  |
| 3 Head form                                    | 18 Hair amount scalp, eye brows, chin, cheeks, trunk, arms, legs, pubes axilla |
| 4 Face shape                                   | 19 Hair texture  |
| 5 Profile nose                                 | 20 Skin color, texture, moisture   |
| 6 Eyes color, set                              | 21 Moles   |
| 7 Ear  | 22 Freckles  |
| 8 Hair form                                    | 23 Wrists and ankles   |
| 9 Hair color                                   | 24 Foot arch   |
| 10 Baldness                                    | 25 Fingers pointed or blunt  |
| 11 Neck  | 26 Nails lunuli, curvature   |
| 12 Larynx                                      | 27 Testes sexual anomalies   |
| 13 Thyroid                                     |  |
| 14 Trunk outline                               |  |
| 15 Fat deposits masculine, feminine, infantile |  |

In order to avoid the usual descriptive terminology which does not lend itself readily to later analysis, comparison and classification, in

<sup>22</sup> A complete medical physical examination was done on each patient

attempt was made to make it more simple and accurate. First a system of  $+$  and  $-$  signs was used to indicate average ( $+$ ), more than average ( $++$ ), and excessive ( $+++$ ), with ( $+-$ ) less than average and ( $-$ ) absent. This was more concise than describing the amount of hair and fat in adjectives and was more convenient in the final analysis. Secondly, diagrams were used to obtain a uniformity of detailed observations, with the personal element of the observer reduced as much as possible and therefore with a greater possibility for the checking up of results by other observers.

The following diagrams were used. The schematic facial outline types are those of Kretschmer (fig. 3). The trunk outlines are adapted from photographs of patients, illustrating recurring conditions (fig. 4). The outlines of face and head are recorded similarly after observation of a number of individuals with a selection of only the most elementary differences in alignment of features (fig. 5, rear profile and top of head from above; fig. 6, forehead, lips and chin). Figure 7 shows diagrams of hands. Diagrams were also used to aid in recording observations regarding hair form, nose, shoulder blades and ear shape. The diagram for hair form was taken from Sullivan (55) after Martin. The diagrams for nose and ear shape were adapted directly from Martin (56).

In about one-third of the cases photographs were taken showing front view of head and chest, profile of head and chest, and trunk in one or two views. These were numbered and the morphological types recorded independently from the other observations.<sup>2</sup> These diagnoses agreed with the classification made from observation of the patients.

#### BODY TYPES FROM OBSERVATION

Our material is too small to yield any conclusive results as to the frequency of occurrence of physical types. Moreover, the percentages of these types in the general population are not sufficiently known. However, since it is a true random sample which contains representatives of the different type groups, a survey of the percentages is not without interest.

<sup>2</sup> We are indebted to Dr. O. Wirth, Associate in Psychiatry, Johns Hopkins University, for diagnosing these photographs for us according to morphological types independently and without any other knowledge of the material.

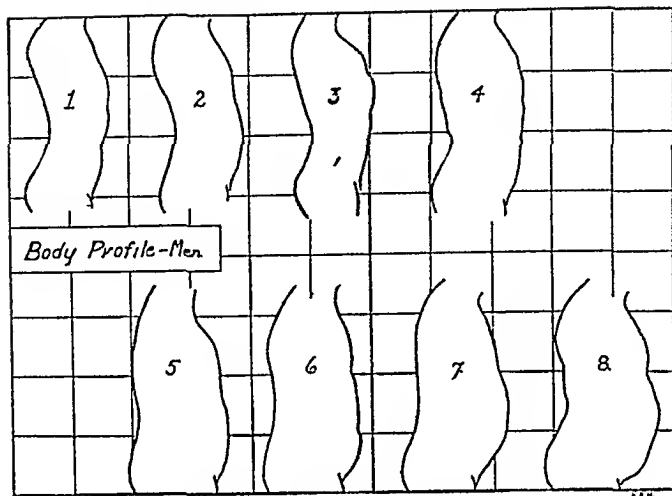


FIG 4 SCHEMATIC REPRESENTATION OF TRUNK PROFILE

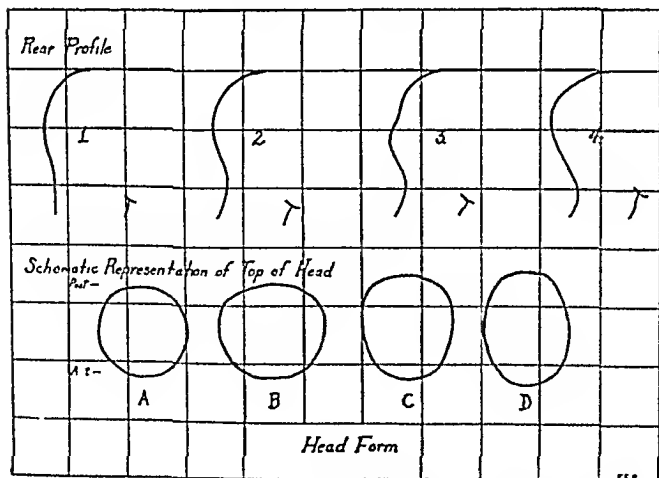


FIG 5 SCHEMATIC REPRESENTATION OF HEAD FORM (REAR PROFILE AND TOP OF HEAD)

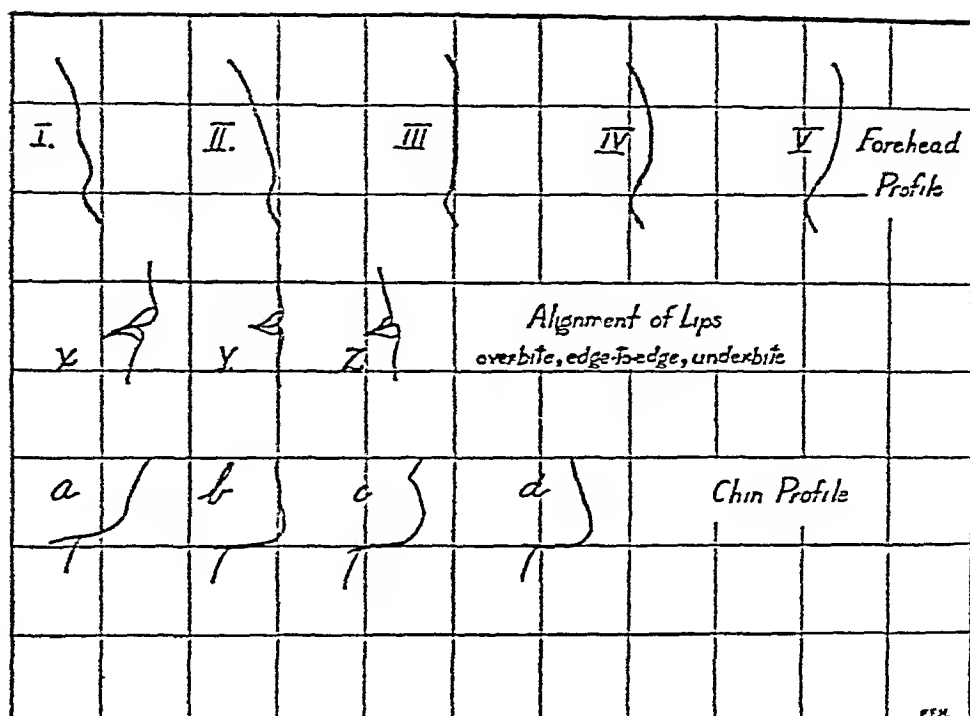


FIG. 6. SCHEMATIC REPRESENTATION OF FOREHEAD, ALIGNMENT OF LIPS AND CHIN PROFILE

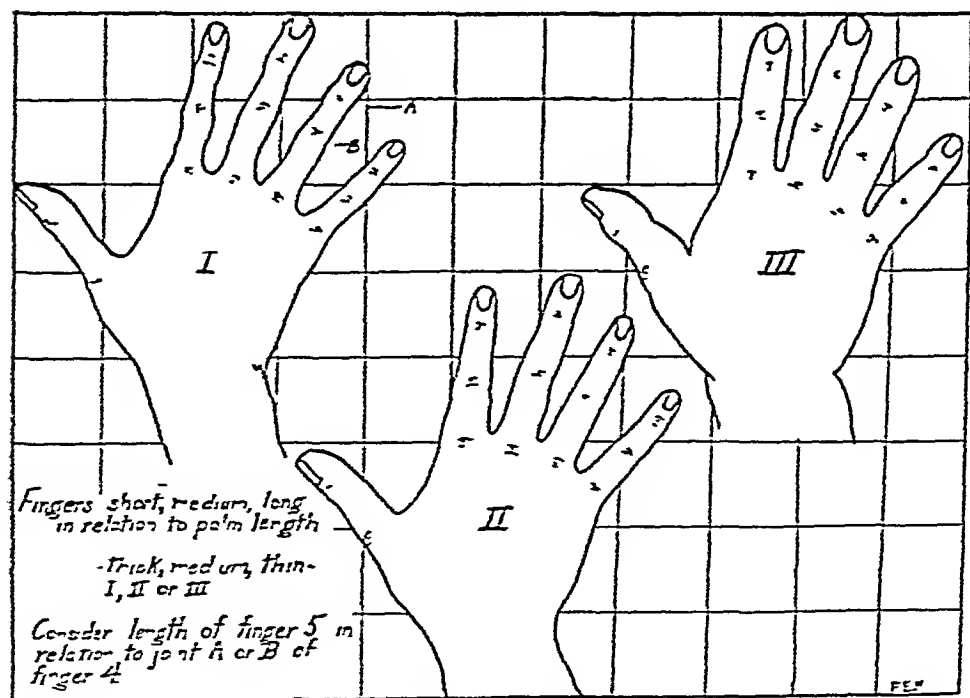


FIG. 7. SCHEMATIC CLASSIFICATION OF HANDS

*Percentages of types in 65 cases*

	<i>per cent</i>
13 pyknics	20 0
7 asthenics	10 8
9 athletics	13 8
18 pyknoid	27 7
15 asthenic athletic mixed forms	23 0
3 unclear	4 6
or	
Pyknic forms	20 0
Pyknoid	27 7
Athletic	13 8
Asthenic Athletic	23 0
Unclear	4 6
Asthenic	10 8

These percentages cannot claim any special significance. However, it is interesting to know that they may suggest a normal distribution curve of symmetrical character (see later).

These percentages include among the others those cases with dysplastic features. Cases with dysplastic features can be subsumed under some of the other types too. They were therefore included in the above tables. Twelve of our cases show dysplastic characteristics, in facial outline, distribution of fat and hair or in general proportions. Of these twelve cases, eleven show marked or suggested feminine distribution of pubic hair among other dysplastic features. Only one has normal distribution of pubic hair (no. 20). His dysplastic features consist mainly of marked disproportion of limb length and stature. The main other findings in his case were mydriasis, eyebrows a little scanty lateralward, small mouth, palate narrow, large hands and long fingers, cyanotic hands and sweaty palms, narrow costal angle, liver dullness not quite two finger breadths below costal margin in right mammary line, gonads normal in size, hypotrichosis of arms and legs, especially thighs, eye grounds very large physiological cupping, discs of good color, lymphocytosis 43 per cent (Dr. Thomas P. Sprunt).

With the exception of one case in the pyknic group (no. 41) and one case in the pyknoid group (no. 58) all of these dysplastic features occur in cases of asthenic, athletic, or asthenic-athletic mixed forms. None of them occur in the three unclear cases. Dividing cases into pyknic, athletic, asthenic, and dysplastic groups, as Kretschmer does, involves the use of two different principles of classification. This

is of importance because a separate correlation of the dysplastic group with psychiatric diagnoses is carried out. The percentage of dysplastic cases was 18%.

#### ANTHROPOMETRIC METHODS

The third series of independent data consists of anthropometric measurements. Fifty-three of these measurements were taken on each patient according to the technique described by Martin (55) (56) and Hrdlička (34).<sup>25</sup>

The following table gives the list of absolute measurements taken.<sup>26</sup>

1. Weight (kilograms)	27. Humerus length
2. Span	28. Radius length
3. Stature	29. Hand length
4. Xiphoid height	30. Hand breadth
5. Symphysis height	31. Palm length
6. Anterior iliac spine height	32. Finger length
7. Tibiale height	33. Nail length
8. Femur height	34. Nail breadth
9. Malleolus height	35. Maximum head length
10. Sitting height	36. Maximum head breadth
11. Trunk height	37. Bizygomatic diameter
12. Horizontal head circumference	38. Bigonial diameter
13. Horizontal chest circumference maximum inspiration, rest, maximum expiration	39. Head height
14. Greatest arm circumference	40. Total face height
15. Smallest arm circumference	41. Upper face height
16. Greatest thigh circumference	42. Nasal height
17. Greatest calf circumference	43. Nasal breadth
18. Smallest leg circumference	44. Ear length
19. Chest length	45. Ear breadth
20. Subcostal angle	46. Ascending ramus length
21. Bi-acromial diameter	47. Horizontal ramus length
22. Bi-iliac diameter	48. Mandible length
23. Greatest hip diameter	49. Gonial angle
24. Transverse chest diameter	50. Interpupillary space
25. Sagittal chest diameter	51. Interocular breadth
26. Arm length	52. Palpebral length
	53. Palpebral breadth

<sup>25</sup> The absolute measurements were taken in the clinical laboratory of the Henry Phipps Psychiatric Clinic with a set of instruments devised by the late Professor Martin of Munich. In connection with these measurements a series of physiological tests was done by Dr. R. S. Lyman which is being worked out independently.

<sup>26</sup> The anatomical terminology is given in preference to the anthropological one, which uses terms such as symphysis, nasion, etc., which are not so familiar to the medical reader.

Thirty-seven different indices were calculated and analyzed in order to find out whether inductively, from a statistical evaluation of anthropometric measurements alone, a grouping of outstanding body types would emerge. These indices are given by Martin (55). The procedure in using absolute measurements and indices was made in two ways. First, frequency distribution curves<sup>17</sup> were plotted for both absolute and proportional measurements. Although the number of cases was too small to expect conclusive results from a frequency distribution, at least an indication of a trimodal frequency distribution might have been expected if the pyknic, athletic and asthenic types were sufficiently distinct. Or further there existed the possibility that if the pyknic and non-pyknic body forms were antagonistic types,

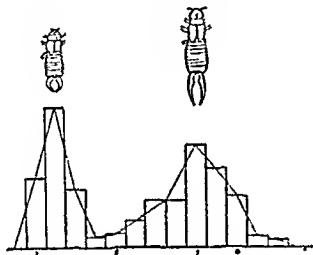


FIG 8 BIMODAL POLYGON ILLUSTRATING DIFFERENTIATION OF TWO SPECIES PLOTTED FROM DATA ON LARWIG  
(From Bateson and Johannsen)

a bimodal frequency distribution curve (cf fig 8) might reveal a suggestion as to the distribution of these two types. No indication of bimodal or trimodal frequency distribution was obtained.

Secondly, the measurements obtained were compared with the averages and ranges of variation for the pyknic, asthenic and athletic types as given by Henckel (30) (31). An analysis was made of the measurements and indices of each patient of the group of this study.

<sup>17</sup> A normal frequency distribution curve, that is to say a curve of chance, is a symmetrical one in which the mode, i.e. the highest point in the curve, and the mean, i.e. the arithmetic average, occur on the same ordinate. A so-called bimodal curve is one which has two peaks and, when representing a sufficiently large sample of data may represent the occurrence of two separate elements in the data considered (see fig 8). Similarly the trimodal curve has three distinct peaks and may indicate three types or elements.



in comparison with the figures given by Henckel as the average, highest and lowest values for each type, as found in his group of cases. This study yielded two negative results. First, on the basis of the measurements used by Henckel, it was not possible to assign the individual cases definitely to one or another of the type groups, secondly, no absolute measurements or indices were indicated as selectively significant in assigning cases in respect to body type, with the exception of the Pignet Index (to be discussed later).

The following is the list of indices which were calculated

- 1 Weight—stature
- 2 Stature—span
- 3 Sitting height—stature
- 4 Trunk height—stature
- 5 Trunk height—span
- 6 Anterior-posterior diameter—lateral diameter chest
- 7 Anterior-posterior diameter—chest length
- 8 Lateral diameter—chest length
- 9 Chest circumference—chest length
- 10 Chest circumference—stature
- 11 Bi-acromial diameter—trunk height
- 12 Bi-iliac diameter—biacromial diameter
- 13 Bi-iliac diameter—trunk height
- 14 Arm length—leg length
- 15 Arm length—trunk height
- 16 Humerus length—femur length
- 17 Tibial length—femur length
- 18 Trunk height—leg length
- 19 Radius length—humerus length
- 20 Finger length—palm length
- 21 Hand length—radius length
- 22 Hand breadth—hand length
- 23 Nail breadth—nail length
- 24 Leg length—thigh length
- 25 Cephalic breadth—cephalic length
- 26 Cephalic height—cephalic length
- 27 Total face height—bizygomatic diameter
- 28 Upper face height—bizygomatic diameter
- 29 Interpupillary space—bizygomatic diameter
- 30 Nasal breadth—nasal length
- 31 Ear breadth—ear length
- 32 Cephalic height—cephalic breadth
- 33 Arm length in per cent stature
- 34 Leg length in per cent stature
- 35 Korperfulle Index (Rohrer)
- 36 Pignet Index
- 37 Morphologic Index

## METHOD OF CORRELATING OBSERVATION TYPES WITH ONE INDEX, "CONSTITUTIONAL INDICES," WEIGHT

The conclusion was therefore reached that these body types could probably not yet be found inductively by anthropometric methods or expressed accurately in anthropometric terms of body proportions. This does not mean that anthropometric methods themselves are not applicable for the distinction of these types, for as in racial anthropology the observation types can be used as a starting point and then correlated with anthropometric measurements. Absolute measurements, such as Kretschmer used in his book, are the least conclusive for such a procedure, for slight differences in absolute measurements may be found in any two groups of individuals, whether they be admissions to a hospital or admissions to a club. In considering the possibility of an index, therefore, which would define the physical habitus of an individual, it is necessary to keep in mind the fact that such a so-called constitutional index should represent the characteristic morphology of the individual as a whole, as contrasted with such indices as the cephalic index, which states the proportion between two measurements of only one part of the body.

As de Giovanni has already pointed out, the impression of the existence of morphological types is dependent on the different size of the body cavities and their relation to the limb length. Naccarati's morphological index is evidently aimed at just this proportional relationship (62). This index, however, is not suitable for psychiatric patients and its accuracy in other constitutional studies may be questioned since in the one index is involved the use of ten different measurements. The fact that two of these measurements may be influenced by subcutaneous fat, variable in most mental patients, increases the opportunity for error. Slight errors may be much magnified in the final result, since nine measurements must be multiplied before being subsequently added. A theoretical criticism of this index might also be raised on account of its form, the mathematical propriety of dividing the product of three measurements by the sum of two others being open to question. More explicit information as to the technique of taking the measurements for this index would be necessary. Measuring a diameter "at the level of the fourth rib"

without further instructions becomes difficult when it is considered that the fourth rib curves in three dimensions, and varies in position during breathing <sup>28</sup>

The variations in weight during psychoses rule out for exact evaluation of the physical constitution of psychiatric patients three other indices which have been used as an index of the physical constitution, namely.

1. The Becher-Lenhoff Index (Martin (55), p 27)  $\frac{\text{Length of anterior trunk wall}}{\text{Waist circumference}} \times 100$
2. The height-weight index of build (Buffon, Rohrer, Bardeen (4))  $\frac{\text{Weight}}{\text{Stature}^3}$
3. The Pignet Index (68)  $\text{Stature (cm)} - [(\text{chest circumference (cm)} + \text{weight (kgm)})]$

The Becher-Lenhoff Index contains as one of its components the waist circumference which is dependent on the state of nutrition of the individual. The Rohrer Index and the Pignet Index contain weight itself. Of these two the Pignet Index requires particular attention since it has been quoted by Kretschmer as an anthropometric confirmation of his findings. Kretschmer also reproduces the table obtained by Henckel (Kehrer and Kretschmer (39), p 179). Three objections can be raised against the Pignet Index as an accurate anthropometric method for the study of the morphological constitution. First it compares a linear with a non-linear measurement (weight), secondly, its accuracy is not beyond doubt since one centimeter is regarded as equivalent to 1 kgm of body weight. A variation of 1 cm in chest circumference can easily occur in two successive examinations. More important than these two is the weight factor. Weight, which is a component of the index, changes considerably in the course of many psychoses so that evidently the index gives different values at different stages of the disease. The weight of both manic-depressive and schizophrenic patients tends to be influenced very much dur-

<sup>28</sup> This index has been used by Dr F. Shaw (80) in a recent study. His data are not significant since no figures regarding the range of variations are given. Aside from this fact, the significance he attaches to the bimodal curve obtained from a frequency distribution of his index values may be questioned. The difference between the two peaks of this curve (which he interprets as definite evidence of the existence of two body types) is numerically one hundred points. Naccarati (62) states that "an error of one-half centimeter plus or minus would cause a change of fifty counts in the index" (p 21).

ing the course of the psychosis In Henckel's study (30) (31) this error is considerably increased by the fact that while his schizophrenic patients were examined during their stay in the hospital (i.e., during the psychosis) a large number of his manic-depressive patients were examined after recovery when the patients were asked to return to the dispensary Thus the evaluation of the Pignet Index in manic-depressive cases was influenced by the fact that the majority of the patients with manic-depressive psychoses as a rule gain weight in the course of recovery, and some in fact to a very considerable degree and with great regularity Kolle has clearly recognized this error without, however, finding a means of evading it (Kolle (41)) He substituted the weight on admission for the weight taken at the time of examination This method neglects the fact that the period of illness before the patient seeks admission to the hospital varies of course greatly in different patients and they may, and often do, lose a considerable amount of weight at that time Figure 11 illustrates the possible variations of weight during the course of recovery The patient (no 10) gained 74 pounds (or 33.8 kgm) from the date of his admission on June 30 to March 15 His best weight was slightly more than 250 pounds about two years before admission This patient was from observation a clear pyknic type, not very conspicuously fat, he was a well-built actor

Henckel assumed that the following averages and ranges of variation of Pignet Index values correspond with the morphological types in mental patients

	AVERAGE	RANGE OF VARIATION
Asthenic	+34.3	(23.0- 54.2)
Athletic	+11.9	(10.6- 21.8)
Pyknic	-5.5	(-34.8-+12.2)

Three examples may be sufficient to show the inaccuracy of this method

1 Patient no 15 Weight on December 22, 45.91 kgm His Pignet Index was 33.7 According to Henckel's figures this should signify an asthenic constitution During the course of recovery from his depression he gained weight and reached by May 12 the weight of 60.0 kgm This influences

the Pignet Index to the value of 196, which according to Henckel would signify an athletic constitution (see fig 9)

2 Patient no 6 Weight on March 4, 59.0 kgm. His Pignet Index was

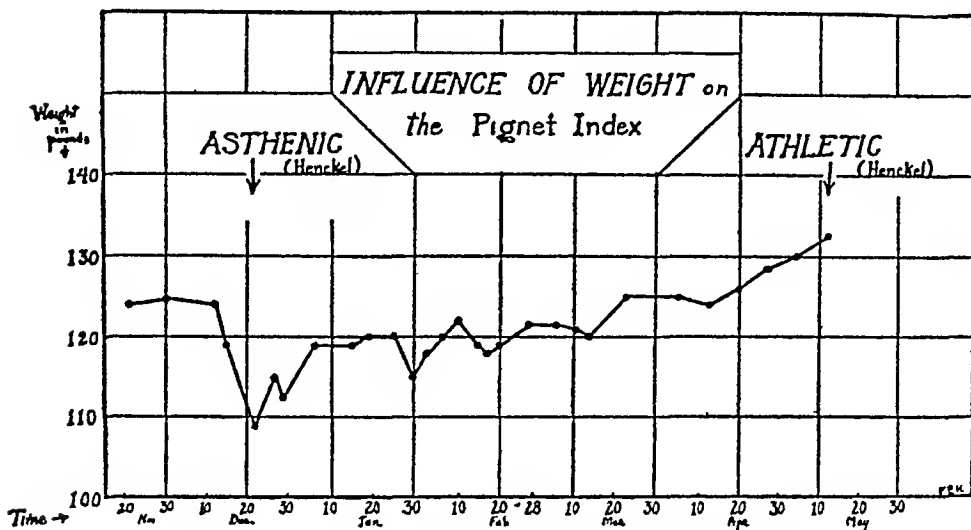


FIG 9 INFLUENCE OF WEIGHT ON THE PIGNET INDEX I

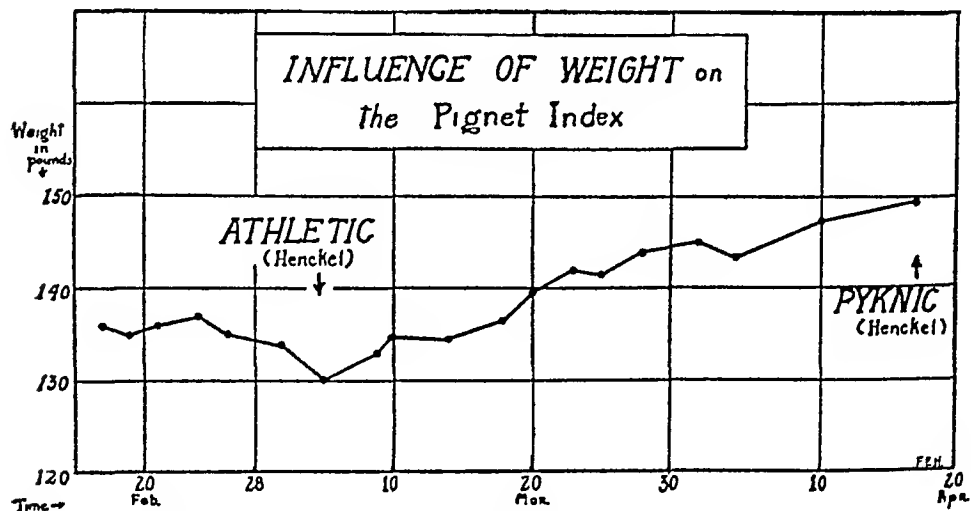


FIG 10 INFLUENCE OF WEIGHT ON THE PIGNET INDEX II

+18.7. This figure would place him, according to Henckel's figures, in the athletic type group. By April 17 he had gained during the course of recovery from his depression to the extent of weighing 68.0 kgm. His Pignet Index calculated for April 17 was therefore +9.7. In other words,

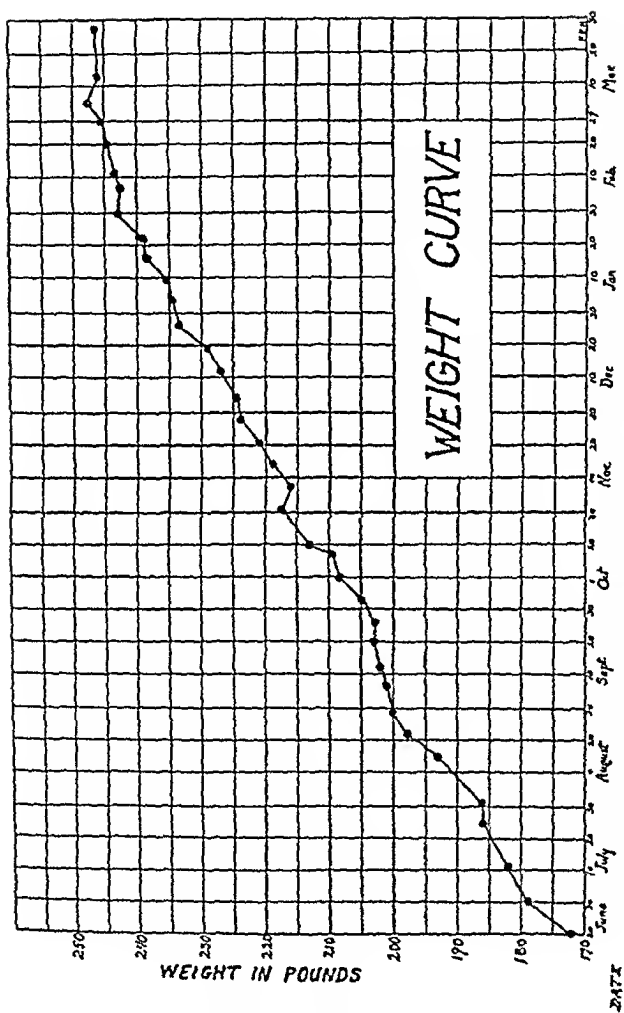


FIG 11 WEIGHT CURVE ILLUSTRATING REGULAR INCREASE OF WEIGHT IN PATIENT RECOVERING FROM A FOURTH ATTACK OF DEPRESSION  
Influence of weight on Pignet Index III

according to Henckel, he had changed from the athletic type to the pyknic type, merely by gaining weight (see fig 10)

3 Patient no 10 Weight on June 20, 78.2 kgm His Pignet Index was  $-2.9$  He gained weight very regularly so that by March 27 his weight was 112 kgm His Pignet Index therefore had changed from  $-2.9$  to  $-36.7$ , that is to say to a value beyond the range of variations given by Henckel for the Pignet Index He remains still of the pyknic type, although the index values changed so enormously, because beyond the pyknic Henckel has no other type (fig 11)

If we assume a patient with stature 164.9 cm, chest circumference 87.0 cm, weight 66.0 kgm, the Pignet Index would be 11.9, i.e., the average value for the athletic type according to Henckel If this patient gains 17.4 kgm, a possible change of weight in the course of a psychosis, his Pignet Index will become  $-5.5$ , or average pyknic If on the other hand this same patient loses 22.4 kgm, his Pignet Index becomes 34.3 or (according to Henckel) reaches the average value for the asthenic type Such considerable changes of weight are not at all infrequent in mental disease However, very much smaller weight changes influence the Pignet Index values to such an extent that (according to Henckel's figures) an individual would be transposed from the boundary of one group to that of another, even though he might not reach the average value for that group.

It seems evident therefore that anthropometric indices which contain weight as a component are not very suitable for exact evaluation of the morphological habitus of mental patients, although they may have proved very useful for classifying the degrees of fitness of recruits Index valuations containing weight can be used only if the weight curve throughout the psychosis from the onset, not only from admission to the hospital, is recorded.

If attention is drawn here to the fact that weight is a source of error in so-called constitutional indices, it is not implied that weight itself may not be of importance as a constitutional sign In fact changes of weight are probably one of the most important constitutionally determined physiological reactions It is a common medical experience that certain people are constitutionally apt to gain weight under conditions when other people do not In mental diseases it is

sometimes striking how psychopathological reactions which in many ways are similar show different weight curves during the psychosis Kraepelin reproduces in his text book ((47), p 1229) two curves of

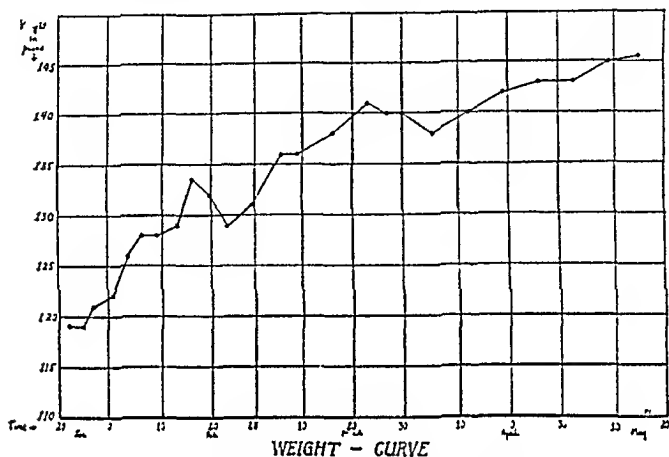


FIG 12 REGULAR WEIGHT CURVE DURING MANIC ATTACK

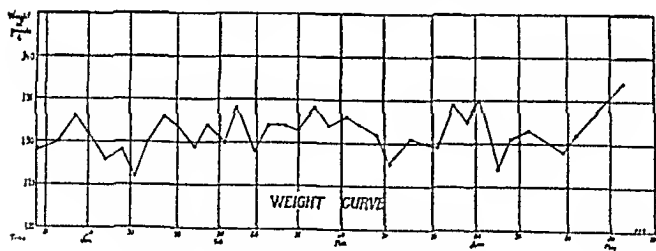


FIG 13 IRREGULAR WEIGHT CURVE DURING MANIC ATTACK

manic patients—one regular, one very irregular. He assumes for the explanation of the irregular weight curve that the manic attack was composed of many small attacks. Figures 12 and 13 show the weight



curves of two patients with predominantly manic excitement from which both recovered completely. The first curve is fairly regular, the second very irregular. The first patient suffered from a manic excitement with religious grandiose delusions and an episode with auditory hallucination. The second patient suffered from a manic excitement complicated by dysmnestic and certain schizophrenic-like reactions. His sister suffered from a recurrent stuporous reaction with a normal interval of about ten years. The first patient was of pyknoïd habitus. The second was of athletic habitus. It is possible that the differences in the weight curve of different mental patients are at least related to the morphological constitution in general. The physiology of the loss and gain of weight in mental diseases is not yet at all clear. From our observation it seems possible to make three factors responsible for weight changes: first, the variation in the actual intake of food, secondly, the often-called endogenic disturbances of metabolism, which according to Reichardt (72) are probably due to a disorder of the central nervous system, thirdly, a constitutional factor which may be correlated in some way with the morphological constitution. In different psychoses these three factors are involved in varying degrees. Reichardt (72) has observed greater endogenic weight changes in schizophrenia than in manic-depressive psychoses (p. 339). An old observation by Nasse (quoted by Rosenfeld (64)) is of interest in this connection. He found that patients who had suffered from previous psychotic attacks tended to show less change of weight during the psychosis. It seemed to him that a constitutional disposition to mental disease may have a certain connection with only slight changes of body weight. In this form Nasse's remark is probably not correct, as is shown by the weight curve of patient no. 10 (fig. 11), who suffered from his fourth recurrent depression each of which was accompanied by considerable loss of weight. Nevertheless there may be a difference in the weight changes of patients with many recurrences and those with only one attack (according to Pollock (69) more than 50 per cent), on the basis that recurrence of attacks may be regarded as a constitutionally determined sign correlated more frequently than other manic-depressive reactions with a characteristic bodily habitus.

# A NEW ANTHROPOMETRIC INDEX, CHARACTERISTIC "TYPES" AT ENDS OF FREQUENCY CURVE

Starting primarily from the morphological conceptions of the Italian school (de Giovanni, Viola) an attempt was made to construct an anthropometric index which would indicate in toto the variations in relationship between trunk cavity and limb length. The greatest difficulty is to obtain measurements indicating the morphological development of the trunk cavity from skeletal points alone and without reference to factors influenced by weight. The skeletal part of the thorax and the trunk height were used as the skeletal substratum of the three-dimensional volume of the trunk. The trunk volume was therefore expressed as the product of three measurements

- 1 Transverse chest diameter
- 2 Sagittal chest diameter
- 3 Trunk height

In order to obtain the relation to limb length the product of these three measurements was combined with the length of the leg. The measurement of the leg length is an indication of the limb length because the ratio of arm to leg length is one of the most constant of human proportional relationships. The formula of the index is therefore

$$\text{Index} = \frac{\text{Leg length} \times 10^3}{\text{Transverse chest diameter} \times \text{sagittal chest diameter} \times \text{trunk height}} \times 100$$

All measurements are expressed in centimeters. The leg length is multiplied by  $10^3$  to bring it from the linear to the cubic dimension and in this way relate it mathematically to the cubic denominator, composed of the product of three linear measurements. The quotient is multiplied by one hundred in order that the result or index may be expressed without decimals. In figure 14 the sixty-five cases are represented in a frequency distribution curve. The abscissa gives the values of the index, each number corresponding to the values from that number to the next higher one, for example in the ordinate column erected over two hundred and forty are all cases with index values from two hundred and forty to two hundred and fifty-five. The

individual cases are plotted on the ordinate. The body types are specified in the key. It will be seen that *the values of the index are in definite relation to the body types obtained from observation.* On the

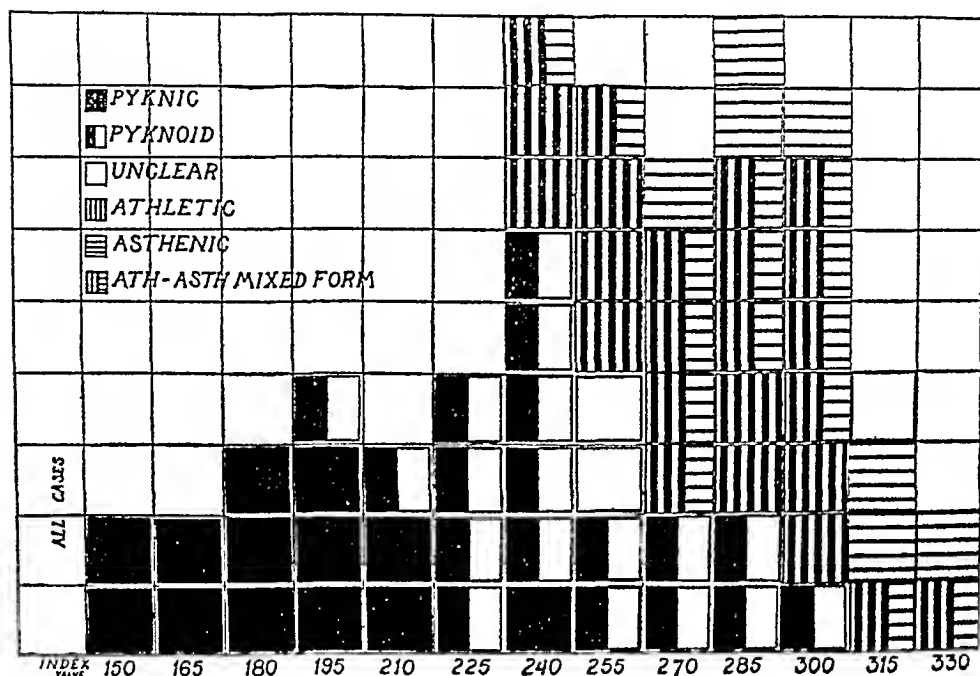


FIG 14 FREQUENCY DISTRIBUTION OF 65 PATIENTS ACCORDING TO THEIR INDEX VALUES, SHOWING THE CORRESPONDENCE BETWEEN INDEX VALUES AND OBSERVATION TYPES

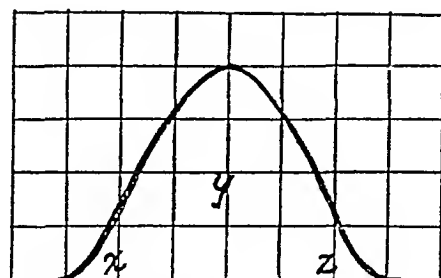


FIG 15 A NORMAL FREQUENCY CURVE

left side, where the lowest index values occur, are the pyknic types. At the right side, where the highest index values occur, are the asthenic types. There is no overlapping of asthenic and pyknic types. They are separated by the group of cases with index values ranging from

two hundred and fifty-five to two hundred and seventy, in which there are neither pyknics nor asthenics. In the middle are the pyknoid and athletic types, and the asthenic-athletic mixed forms. The pyknoid types tend to the lower, the athletic to the higher, index values. The asthenic athletic mixed forms tend to higher values of the index than the athletic types. The three cases which were unclear as to classification with regard to body types from the description alone are scattered from the middle to the right side. None of them occur in the pyknic group. Pyknic and non-pyknic forms are clearly differentiated.

The chart indicates a *gradual transition from lower values to higher values of the different clear and mixed types represented*. This seems to be a significant finding because it is established on anthropometric measurements alone without deduction from general types. The chart seems to indicate also that with a sufficiently large number of cases the distribution of body forms would present a normal frequency curve. This distribution would be represented on a curve like that in figure 15. The most clearly differentiated forms would be at X and Z, the less characteristic forms, intermediate types and gradations in the portion of the curve designated Y. This distribution would explain why analysis of varied anthropometric data in search of indications of the existence of out-standing types (indicated by frequency distributions giving bi- or multi-modal frequency distribution curves) proved unsuccessful.

The general distribution according to values of the index seems to coincide in principle with the results of investigations by Viola and also by Bauer, who used the descriptive types of Sigaud. Viola (6) found among four hundred male individuals of Northern Italy much overlapping between the megalosplanchnic and normosplanchnic habitus on the one hand and between the normo- and microsplanchnic on the other (according to his classification). Bauer (6) who recorded the types of Sigaud in two thousand cases at the Vienna Dispensary also found a preponderance of so-called mixed forms. From our material the smaller number of well-defined morphological types in comparison with the others seems well established.

It is possible—even probable—that if a sufficiently large number of cases were collected and classified according to the index, the resulting curve would be asymmetric, or a so-called skew curve, with the peak

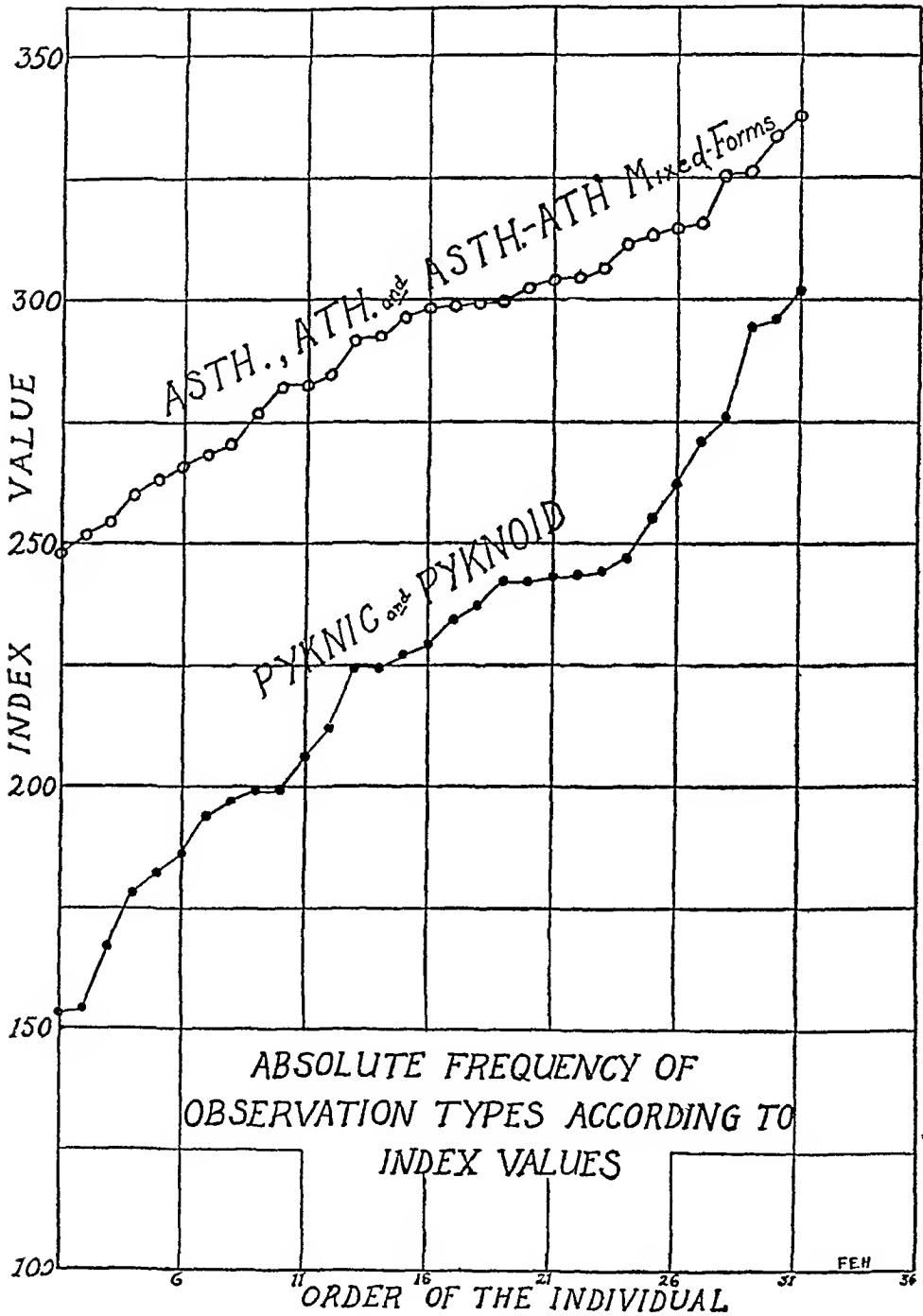


FIG 16 ABSOLUTE FREQUENCY CURVES OF OBSERVATION TYPES ACCORDING TO INDEX VALUES, ILLUSTRATING THE DIFFERENCE BETWEEN THE PYKNIC AND PYKNOID AND THE ASTHENIC-ATHLETIC FORMS OF BODILY HABITUS

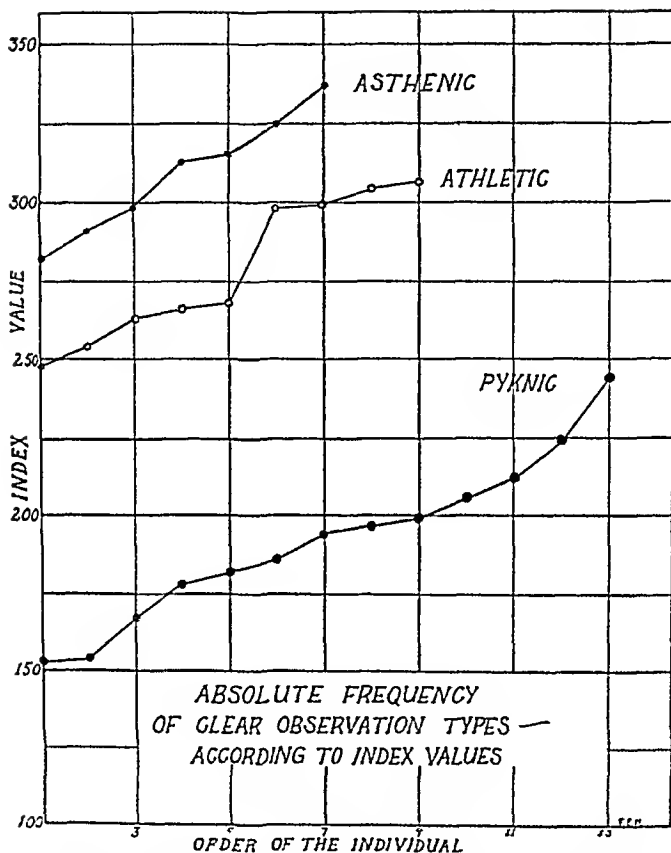


FIG 17 ABSOLUTE FREQUENCY CURVES OF CLEAR OBSERVATION TYPES ILLUSTRATING DIFFERENCES IN INDEX VALUES BETWEEN THE ASTHENIC, ATHLETIC AND PYKNIC TYPES

not in the middle but toward either side. This study is not intended for these anthropological problems, but only for clinical ones, and the material is also too small to allow definite percentage conclusions.

Moreover it deals only with a selected group of the population, namely individuals afflicted with mental disease, while the proportions of the general population are not accurately known

In figure 16 the asthenic, athletic and asthenic-athletic mixed forms are contrasted graphically with the pyknic and pyknoid forms in ogive curves<sup>29</sup> according to their index values. The two curves are entirely separate and do not show any tendency to cross. There is a considerable interval between any two contrasted points along their course. This can be taken as an indication that the material does not represent one homogeneous type, but that on the contrary at least two types are present. If the two ogive curves represented cases of a homogeneous type a crossing or intermingling of the two curves would be expected.

In figure 17 the absolute frequency of those types which appear from observation as more or less clear is represented according to their index values. The pyknic type forms the lowest curve, the athletic type the middle, and the asthenic the highest curve. This chart indicates that the anthropometric values of the index separate these three types, the distinction between the asthenic and pyknic type being very considerable and beyond doubt. The curve of the athletic type lies between the two, but definitely nearer the asthenic, indicating that with regard to trunk volume and limb proportions the athletic type is nearer the asthenic than the pyknic type. Thus the anthropometric values of the index permit an exact statement which is in conformity with the more general impression received from observation. It is improbable that the distribution on this curve is due to the small number of cases.

The average index value and the range of variation for each morphological group are as follows

	INDEX	RANGE OF VARIATION
Asthenic	309	(282-337)
Athletic	278	(248-306)
Pyknic	192	(153-244)

<sup>29</sup> The ogive curve, so-called by Galton who devised it, has been chosen as the graphic method of representing the absolute frequency distribution. According to this method the measurement (in this case the index) is plotted on the ordinate axis, the absolute frequency = order of the individual, along the abscissa. So at equal intervals along the abscissal axis an ordinate is erected for each individual, representing his index value.

The difference between the index values of asthenic and pyknic types is therefore not only great (117), but there is also no overlapping between the extreme members of the group. The highest pyknic index is 244, the lowest asthenic index is 282. The athletic group is in an intermediate position between the other two.

#### ANALYSIS OF THE VARIOUS COMPONENTS OF THE INDEX

Since the index used contains four different components, each of which may be variable, an analysis of the variation of these components is necessary. The following table gives the average values with the range of variation for each component of the index. The measurements are given in centimeters.

MEASUREMENT	ASTHENIC	ATHLETIC	PYKNIC
Trunk height	49.7(53.1-62.7)	57.0(52.0-60.8)	58.9(51.7-64.9)
Leg length	85.6(78.3-101.6)*	88.2(75.2-92.2)	85.2(77.5-92.5)
$\frac{\text{Trunk height}}{\text{Leg length}}$ index†	66.7(62.5-69.2)	64.9(60.1-71.1)	68.9(61.9-79.0)
Transverse chest diameter	25.6(24.3-28.7)	28.0(26.0-29.8)	31.3(28.7-34.6)
Sagittal chest diameter	19.1(18.1-20.7)	19.9(17.8-23.5)	24.4(22.0-29.0)

\* Case no. 20, see below.

† Since the absolute measurements are much less significant the trunk length expressed in percentage of the leg length is added to the table giving the measurements contained in the index.

It will be seen that the trunk height shows considerable difference. The absolute leg length shows practically no difference between asthenics and pyknics, although under the asthenics is included case no. 20, a case with dysplastic body form, his legs being disproportionately long. The trunk height-leg length index shows a 2 per cent difference between each group. A considerable difference is also present in the chest diameters. It seems of significance that those components of the index which show the most marked differences, namely, trunk height and chest diameter, show an increase in value from asthenic to athletic to pyknic, the athletic being in the middle just as in fig. 17.



## AVERAGES OF SOME OTHER ANTHROPOLOGICAL DATA

Our interest being primarily a clinical rather than an anthropological one, we are less concerned with anthropological details. Nevertheless, some other measurements seem to add not insignificant characteristics, and may be of interest for a morphogenetic interpretation of these types. The following averages and ranges of variation are therefore given<sup>30</sup>

	ASTHENIC	ATHLETIC	PYKNIC
1 Body surface (in sq. m.)	1 65(1 49-1 97*)	1 71(1 41-1 90)	1 96(1 72-2 29)
2 Subcostal angle (in degrees)	55 0(50 0-60 0)	64 5(50-75)	73 0(55-90)
3 Head circumference (in cm.)	56 4(54 5-58 0)	56 3(54 2-59 0)	57 5(53 4-60 5)
4 Cephalic length-breadth index	76 9(69 9-86 1)	78 6(75 1-85 2)	79 4(77 5-80 9)
5 Cephalic height-length index	68 7(63 4-74 6)	71 1(65 7-78 2)	70 1(65 6-74 9)
6 Cephalic height-breadth index	88 3(81 4-100 0)	90 6(81 2-99 3)	88 5(78 8-93 6)
7 Bi-iliac diameter (in cm.)	28 0(25 1-31 2)	29 1(26 7-34 0)	32 2(28 9-36 5)
8 Bi-acromial diameter (in cm.)	36 2(33 3-39 4)	39 1(35 5-41 9)	39 3(33 9-43 0)
9 Bi-acromial diameter/bi-iliac diameter index	1 31(1 17-1 41)	1 34(1 23-1 41)	1 23(1 07-1 35)

\* Case No. 20 (dysplastic). The next figure is 1 69.

It will be seen that there is a marked difference between the pyknic and asthenic body types with regard to body surface and to subcostal angle, the athletic type taking an intermediate position in relation to the measurements of the other two body forms. The head measurements do not show any marked distinction. Measurements of considerable interest because of the relative and absolute proportions they indicate, are those of the bi-iliac and bi-acromial diameters. (The bi-iliac diameter is taken at the outer border of the iliac crests, according to Martin's technique.) The preceding figures show that the absolute measurements of the pyknic are greatest. However, con-

<sup>30</sup> These figures, based on a relatively small number of cases, can have significance only as indications of the proportions to which the types tend, and cannot be expected to adequately delineate the types.

sideration of the relationship between these two measurements in each type group shows that the pyknic habitus has least difference between shoulder width and pelvic breadth (considering these measurements as indicators of these two dimensions), while the asthenic comes next, and the athletic has the greatest difference between these two dimensions. It will be recalled that the pyknic type was described as having a barrel-like trunk, largest in the middle dimensions, and returning at the pelvis to proportions comparable with the shoulder breadth. It is also of interest to note that the impression of the broad shouldered trapezoid-like trunk of the athletic is upheld by these figures. The figures for the asthenic type indicate a more slender type, especially as contrasted with the stocky pyknic form.

Considering the anthropological significance of data concerning hair and eye color, the fact that analysis of these data in the types of habitus considered here yielded no results in any way significant, is not without interest. Regarding complexion the generalization can be made from our material that as a rule the pyknic type has a fresher and more ruddy color, and a clearer and more smooth skin, than occurs in the other two types.

#### FACTORS INFLUENCING THE MORPHOLOGICAL HABITUS, THE RACE FACTOR, AGE AND GROWTH, ENVIRONMENTAL INFLUENCES (OCCUPATION)

A number of factors influencing bodily habitus have to be considered. That racial distribution is not a causal factor for these morphological types as has been claimed by Stern-Piper (83)<sup>41</sup> is apparent from our material, which is an example of the racially heterogeneous American population. In most cases both maternal and paternal extraction could be obtained. Our patients represent parental extraction of the following character: Scotch, Irish, English, Dutch, French, Norwegian, North German, South German, Welsh, Swedish, Canadian, Portuguese, Russian, Italian, Polish and Czecho-Slovakian. It is possible, in fact very likely, that different races show a different distribution of these body types. Stockard (85) believes that the English people of the upper class show more often the linear type,

<sup>41</sup> Compare also von Rohden (74) who expresses the opposite view.

Germans of the upper class more often the lateral type. Whether they occur among all races is not yet established

Much more important is the age and growth factor. The original assumption of Sigaud that his morphological types are unchangeable during life had to be given up. Viola believes that the longi- and brachy-types are unchangeable and independent of changes with age. Zweig (95) found that although a definite tendency to the four Sigaud types is already apparent in youth, they are not so unchangeable in the course of life as Sigaud had claimed. Especially the digestive habitus shows progressive increase with age. Bauer (6), p. 1086, also found age displacement of the Sigaud types. Brugsch (11) found that the narrow chested type develops to a normal chested type in one-third of all cases from the age of twenty-five to thirty-five. The normal chested type can develop with advancing age to a wide chested type (pathological emphysema type). Florschütz (21) found in a large statistical material that asthenic individuals do not lose that type, but that with advancing age the type becomes even more apparent. Mills (59) distinguishes dominant types (hypersthenic and asthenic), major types (hypersthenic, sthenic, hyposthenic and asthenic), and six sub-types. According to his observations on over one thousand individuals, bodily changes may lead to a reclassification of an individual with regard to a different sub-type, but no changes occur indicating a reclassification as to major type.

The environmental influences on morphological habitus, which of course become apparent at different ages, are considered in the researches of Verschner on the anthropological characteristics of single-ovum twins (89). According to his findings, which, however, are not final and not in agreement with some other observations, the following characteristics are little affected by environmental influences in the widest sense: stature, length of extremities—absolute and relative to stature, ears, nose, eyes. Much influenced are the following: length, breadth, depth and circumference of trunk, excluding shoulder and thorax breadth, body weight, length, breadth and length-breadth index of skull. The difference between twins does not essentially increase with further years after the end of the age of growth.

In our material the age distribution is as follows<sup>22</sup>

	AVERAGE	RANGE OF VARIATION
<i>According to types</i>	<i>Years</i>	
13 pyknics	45 1	(24-59)
7 asthenics	29 0	(16-52)
9 athletics	28 7	(20-51)
<i>According to diagnosis</i>		
19 predominantly affective	36 2	(18-65)
25 predominantly schizophrenic	28 6	(18-39)
21 other cases	38 8	(22-56)

The pyknic type is more frequent with advancing age. Bauer found this also for the digestive type of Sigaud. For clinical correlations this is of special importance since manic-depressive psychoses occur more frequently in middle age. Mollenhoff (60) has pointed out the importance of the age factor for these correlations. He found the asthenic type more frequently among his young patients and the pyknic type more frequently with advancing age.

From the anthropometric analysis the conclusion was also reached that the age factor is very important and that there is a far-reaching age displacement of body types. That age on the other hand should be the only factor responsible seems extremely unlikely. There are cases of definite pyknic habitus with low index at an early age, and of pronounced asthenic habitus with high index at an advanced age. Moreover, as Kretschmer (45) has pointed out, there are details of observation which according to clinical experience change very little with age, for example the form of the hand and head, and the color of the skin.

The ratio of the body length below the symphysis to that above the symphysis shows very marked changes with growth. The line dividing the stature in half in the infant lies considerably above the symphysis. In adult age the length of the upper part of the body (above the symphysis) becomes greater than the height from the symphysis to the floor. According to studies of Fischer and Hoffmann (20) on three hundred and sixty healthy soldiers, this constant predomi-

<sup>22</sup> See also page 430

nance of the length of the upper part of the body is reached in one hundred per cent of the individuals by the twenty-ninth year. In our material the exact ratio of the upper to the lower part of the body is variable (when considered in reference to age). At the age of twenty-nine it may be assumed that at least the maximum growth of the thorax is completed. For these reasons separate correlations between index values and psychiatric diagnosis were made with the exclusion of all patients under twenty-nine.

For dysplastic features the age factor is less significant. The pubic hair, for example, according to the painstaking statistical studies of Scheidt (77) shows the full virile growth about the eighteenth year. The distribution type is finally established by the end of the second decade. The average age of patients in the dysplastic group is thirty, the range of variation 16 to 51.

The influence of occupation seems on the whole of little significance for the essential morphological characteristics. With regard to occupation our material is divided according to the old and somewhat arbitrary classification of Gould, which nevertheless is sufficiently useful.

- I Those who work with the head
- II Those who work mainly with the arms
- III Those who work with arms and legs (sailors)

Our material falls into the following classes:

<i>According to diagnosis</i>			
All cases	I	.	35
	II	.	27
	III	.	3
Manic-depressive, I	.	.	19 (all)
Schizophrenic	I	.	9
	II	.	14
	III	.	2
Organic	I	.	2
	II	.	7
	III	.	1
Psychopathic personalities and psychoneuroses	I	.	5
	II	.	6
	III	.	0

*According to types*

13 pyknic	I	5
	II	7
	III	1
9 athletic	I	4
	II	5
	III	0
7 asthenic	I	5
	II	1
	III	1

*According to source*

	<i>Henry Phipps Psychiatric Clinic</i>	<i>Spring Grove State Hospital</i>
Manic-depressive	18	1
Schizophrenic	11	11
Organic	7	3
Psychopathic personalities and psychoneuroses	9	2
	<hr/> 45	<hr/> 20

It would seem that the affective cases belong more to the group of mental workers. This agrees with Stern (82) and Mollenhoff (60), but is in our material partly explained by the fact that the patients come from two sources drawing patients to some extent from different social strata.

#### CORRELATION OF PSYCHOSES AND PREPSYCHOTIC PERSONALITIES WITH INDEX VALUES AND BODY TYPES FROM OBSERVATION

It is possible then to distinguish from the morphological aspect different groups in this series of sixty-five cases. For clinical correlation we are now in a position to dispense with the body types obtained deductively from the general impression and can substitute the inductive method of comparing the anthropometric values of the index with psychiatric diagnostic groups, without knowledge of what the general type impression from observation would be.

In table 2 all sixty-five cases are represented with a serial number, initials, order in the four diagnostic groups, special psychiatric diagnosis, body type from observation, index value, and incidence of dysplastic features.

It may be assumed from the distribution of the cases according to index values (see fig 14) that the extreme values of the index may be regarded as characteristic recurring body forms which impress one as morphological body types. If the whole range of index values in the first two psychiatric diagnostic groups is divided into four equal parts, the opportunity is created to determine what psychopathological reactions have an affinity to the index values which are very low (lowest quarter) and those which are very high (the highest quarter). In the range of the lowest quarter of the index values there are only three patients with the following index values 154, 167, 182. All these three patients belong clearly to the manic-depressive reaction type. The first one (no 10) was admitted in his fourth depressive attack. The second one (no 16) was admitted in his second depressive attack. The third patient (no 6) suffered from a depressive reaction. In the highest quarter of the range of index values there are, leaving out those with dysplastic features, twelve patients. Of these twelve patients seven belong to the schizophrenic reaction type (nos 25, 39, 21, 43, 35, 22, 23). Two belong to the predominantly affective group but are specified as showing schizophrenic features during the psychosis (nos 18 and 19). One case (no 9) occurs in the affective group but is specified as psychoneurotic depression. Only two cases belong to the manic-depressive reaction type without qualification (nos 3 and 11). Both are very young. This seems to point to the conclusion that the lowest index values occur more among the manic-depressive reaction types and the higher index values among the schizophrenic individuals. If patients with dysplastic features are included there is added to the lower fourth one patient (no 41) with the diagnosis schizophrenia and to the upper fourth of the range of index values six patients with dysplastic features (nos 27, 31, 8, 36, 28), all of whom belong to the schizophrenic reaction type with the exception of one (no. 8) who occurs in the predominantly affective group but is specified as showing schizophrenic-like admixtures.

If the index values are now split into thirds it can be determined what psychopathological reaction types occur in the lower third and which in the upper third, including in both groups individuals showing dysplastic features. In the lower third of index values there are six

patients, in the upper third twenty-one patients (including only the first two psychiatric diagnostic groups) Of the group of six patients with low index values, four patients belong to the manic-depressive reaction type (nos 10, 16, 6, 7) The last patient is in this connection of particular significance He suffered for seventeen years from a chronic manic condition from which he recovered with good insight We had the opportunity of seeing this patient during the psychosis, during recovery, and in the normal period after his recovery, and had then occasion to observe him again in his second attack, which was clearly of a manic nature and from which he also recovered completely after about four months<sup>23</sup> Of the two other patients in the lower third of the index values, one (no 41) showing dysplastic features, belongs to the schizophrenic reaction type, the other one (no 24) occurs in the schizophrenic group, but is qualified as an atypical case with anxiety features It is evident again that among the lower index values the affective psychoses are predominant

Of the twenty-one patients occurring in the upper third of the index values there are fourteen with schizophrenic reaction type (nos 30, 38, 25, 39, 27, 21, 43, 35, 22, 20, 23, 31, 36, 28) Three cases occur in the predominantly affective group, but are specified as showing schizophrenic features (nos 18, 8, 19) One case (no 9) in the affective group presents psychoneurotic symptoms Only three patients occur in the manic-depressive group without qualification (nos 17, 3, 11), two of these patients being the two youngest individuals of the manic-depressive group The predominance of schizophrenic reactions in this group with higher values of the index is apparent It is also significant that those three cases in the affective group are included from the morphological aspect in the group with higher index values, which from psychiatric diagnostic principles alone had been previously specified as being somewhat atypical in the affective group because they show also schizophrenic-like reactions It has to be taken into account that the psychiatric diagnoses were put into their final form before the calculation of the index values was completed

<sup>23</sup> This case will be presented in more detail in a later study



If only the more or less clear manic-depressive and schizophrenic cases are selected the following index averages are obtained

	AVERAGE INDEX	RANGE OF VARIATION
All clear manic-depressive cases (11 cases)	233 2	(154 -315)
All clear schizophrenic cases (23 cases)	280 7	(178*-337)

\* Patient no 41 with dysplastic features, the next higher index value is 229

Since, however, the age factor as we have seen is of importance and since the manic-depressive patients usually have a considerably higher average age than the schizophrenic patients this has to be taken into account for the psychiatric correlations

	AVERAGE AGE	RANGE OF VARIATION
	<i>years</i>	
Clear manic-depressive cases	39 3	(18-65)
Clear schizophrenic cases	28 7	(16-39)

If only those cases above and including twenty-nine years are selected (see discussion on page 425) the following index averages are obtained

	AVERAGE INDEX	RANGE OF VARIATION
Clear manic-depressive cases (6 cases)	199 1	(154 -262)
Clear schizophrenic cases (12 cases)	260 3	(178*-315)

\* Patient no 41 with dysplastic features, the next higher index is 229

Correlation of all clear manic-depressive and schizophrenic diagnoses with morphological types from observation (including patients with dysplastic features) gives the following percentages

*In clear manic-depressive cases, all ages*

	<i>per cent</i>
Pyknic .	45 5
Pyknoid . .	36 4
Asthenic .	0
Athletic .	9 0
Unclear . .	9 0

*In clear schizophrenic cases, all ages*

Pyknic	4 3	
Pyknoid	13 0	
Asthenic	17 4	} 78 3
Athletic	26 1	
Asthenic athletic mixed	34 8	
Unclear	4 3	

*In clear manic-depressive cases 29 years and over*

Pyknic	66 6
Pyknoid	33 3
Asthenic	0
Athletic	0

*In clear schizophrenic cases 29 years and over*

Pyknic	8 3	
Pyknoid	25 0	
Asthenic	16 7	} 58 4
Athletic	16 7	
Asthenic athletic mixed	25 0	
Unclear	8 3	

The different diagnostic groups are too small to allow a differentiation according to special types of schizophrenic or affective reaction. However, from the schizophrenic group may be selected all those cases with catatonic phases. Three patients in this group show catatonic symptoms (patients nos 22, 23, 27). All three have indices in the upper fourth of the range of index values (indices 306, 314, 298). Two patients in the schizophrenic group show simple deterioration (nos 28 and 43). Their index values are above 300 (302, 337). Individual correlations of each case may be seen on table 2.

Independent of Kretschmer's researches, Bernger and Düser (8) showed the frequent incidence of eunuchoid and feminine morphological traits in schizophrenic patients. Gibbs (23) found feminine distribution of pubic hair in 13 per cent of schizophrenic patients admitted between sixteen and twenty, which was still present in 13.4 per cent after they were twenty-one or over, but this characteristic was present in only 2.6 per cent of those patients admitted between twenty-one and forty.

Twelve patients of the group of sixty-five considered in this study have dysplastic features. Eleven of these showed among other dys-



The percentage of the incidence of body types in the general population is not accurately known. While the types of Viola, Sigurd, and Kretschmer, and our group with high and low index values, have a certain similarity, no definite conclusions can be drawn with regard to the incidence of types in the general population from studies which have been done according to only one of these classifications (like that of Viola, see p. 415). For this reason the emphasis of this study had to be necessarily on the contrast between the two psychiatric diagnostic groups—the manic-depressive and the schizophrenic. Apart from the relatively small number of cases in this material, a comparison of the percentages obtained by other authors following Kretschmer (see Kehrer and Kretschmer (39) table on p. 174) is not carried out because these percentages based on the observation of types do not sufficiently take into account the displacement of body types due to age. They all contrast schizophrenic with manic-depressive patients, and it may be inferred that the manic depressive group shows a higher average age than the schizophrenic cases, if unselected cases are taken. While from this study it seems apparent that, even apart from the age factor, the pyknic and pyknoïd forms occur more in manic-depressive patients than in schizophrenic cases, and the athletic, asthenic and dysplastic forms occur more frequently among schizophrenic patients as compared with manic-depressive reaction types, yet it does not seem possible as yet to state exactly how far the age factor is of influence. For example, Kretschmer (45) quotes the statement of von Rohden that in nine hundred and thirty-seven manic-depressive cases of various observers who used his (Kretschmer's) method, the percentage of pyknic body forms is 66 per cent. In our group of clear manic depressive cases, the percentage of typical pyknic body forms is only 45.5 per cent. If, however, from this group of more or less clear manic-depressive psychoses, the cases with ages under thirty years are taken out, the percentage of pyknic body types rises to 66.6 per cent (see pages 423 and 429). All the percentages of body types in psychoses, based on observation, have therefore to be taken with the greatest caution on account of the age factor. Correlations should start from exact percentages of body types in the general population. Since this is not possible as yet, two psychotic groups are contrasted which unavoidably, at least as far as

patients observed in psychiatric clinics are concerned, are of different age. Kretschmer has not done justice to the importance of the influence of age. He (39) gives three tables in which his schizophrenic and manic-depressive patients are classified in age groups, but they refer only to chest circumference, Pignet Index, and relation of stature to weight. The age factor, therefore, seems at present one of the most urgent problems of investigation with regard to the morphological constitution in psychiatry.

An attempt was made to make independent correlations between morphological type and prepsychotic personality. Popular belief associates broad and slender body-types with all sorts of mental characteristics and habits. Slender people are supposed to be more often cigarette-smokers, broad people more often cigar-smokers. Lovers of alcohol are supposed to be more broad, abstemious people more slender.<sup>34</sup> Broad people are often regarded as more materialistic and sensuous, slender ones as more idealistic and mystical. There are many examples in folk-lore of similar beliefs. That criminals and "bad men" are characterized by certain physical qualities and are often of dysharmonious growth, was a very widespread popular belief until the advent of the modern moving picture era. Homer depicted Thersites with a generally deformed body and misshapen head. Deficiencies in hair growth are also associated with mental characteristics in popular belief, as shown for example in the French proverb: "Salute from afar the beardless man and the bearded woman."

It is not intended here to discuss in detail the many attempts that have been made to distinguish personality types. None of these attempts have been entirely successful. They are all based on simplifications which do not do justice to the complicated dynamic interplay between the personality and the social setting. From the findings of experimental psychology the human personality as a living entity does not emerge. With the "psychodiagnostic test" of Rorschach constitutional differences between individuals can be found, similar to

<sup>34</sup> Cf. the epigram by J. B. Rousseau (1670-1741)

Toujours ces sages hagards,  
Maigres, hideux et blafards,  
Sont souillés de quelque opprobre,  
Et du premier des Césars  
L'assassin fut homme sobre

though not identical with the intraverted and extraverted types as distinguished by Jung Kretschmer has used the distinction of "schizoid" and "cycloid" personalities. The concept of "schizoid" personality originated from the observation of three classes of individuals: first, the pre-psychotic personality of individuals later suffering from schizophrenic psychoses, secondly, the type of to some-degree distinctive personalities sometimes found in the ancestry of schizophrenic patients, thirdly, a type of psychopathic personality with habitual psychopathological reactions similar to some extent to certain manifestations of the schizophrenic reaction type. The concept of "cycloid" personality has a similar origin. In this way personality types are postulated in relation to clinical entities. The danger of this procedure lies in the fact that these two very expanded groups are found again and again, because nothing else is looked for (Kalin, (38), p. 48). In the form given to them by Kretschmer they do not constitute a new point of view, but rather the latest ramification of the Kraepelinian system of clinical disease entities. The evidently secondary psychological presentation of these two types is based on two not unitary principles called by Kretschmer the "diathetic" and "psyschaesthetic" proportions. There is a great variety of individuals classified under those two types, which makes it doubtful whether one can speak of them as personality "types." Certain individuals described as schizoid personalities can be designated from a clinical point of view with the same justification, and from a therapeutic point of view more profitably, as psychoneuroses. It seems that the indiscriminate use of the term "schizoid" may do a great deal of harm. This term has the double meaning of being in fact closely related to schizophrenia, as in Kalin's theory of the mode of hereditary transmission of schizophrenia and of being in some way psychologically similar to it, as in Bleuler's distinction of schizoid and syntonie.\*

In everyday life personalities are judged usually by the affective attitude toward the environment, especially other individuals and the social group. It seems that with regard to the affective attitude it is possible to distinguish among many individuals two directive tendencies, more or less evident throughout the course of life. Some individ-

\* The word *syntonie* conveys the meaning of a *being tuned together*, a harmony between the individual and his environment which is not the distinctive mark of these individuals who have rather a tendency in their affective life to react together with others, *harmoniously or otherwise*. (See later discussion.)

uals look for satisfaction in contact with others, the emphasis of their affective experiences and reactions being always on the personal environment. Not only do they react emotionally to the experiences of life, entailing coordination or disagreement with others, but they are always fundamentally in affective contact with the personal and social environment. There are other individuals, on the other hand, who find satisfaction in difference, in detachment and isolation from the personal and social environment. The emphasis of their emotional experiences is much less on the other personalities with whom they come in contact during the course of life, and more on the reactions and ramifications of their own mental experiences, both intellectual and imaginative. One may speak of the first group as the syntropic, because the tendency of the affective attitude of individuals included there is to association and contact with the personal and social environment, the second group, with affective attitude characterized by a satisfaction in difference and separation from emotional relationship with other individuals of their environment, one may speak of as idiotropic.<sup>35</sup>

These characteristics are not sufficient to constitute personality types, but are sufficiently distinct to denote antagonistic directive tendencies. The assigning of an individual to the idiotropic or syntropic group must be dependent upon the evidence of more or less habitual reactions in the course of life. Only very rarely do individuals change from one of these extremes to the other. It is not to be understood that syntropic individuals are always well-adapted and in accordance and harmony with the social environment. On the contrary, they are often not well-adapted, but whatever psychological reaction may lead them to social estrangement the fundamental affective tendency to influence the environment, to "get something across," to find satisfaction and consolation in an emotional setting involving other individuals, is often apparent. In the treatment of syntropic individuals with depression one often finds the tendency to suffer not alone, but through and with others.<sup>36</sup> Idiotropic individuals, on the other hand, need not be badly adapted, but may show good social adaptation. This is, however, fundamentally due to lack of

<sup>35</sup> From the Greek word *tropos* meaning turn, turn of mind, affective tendency, and from the Greek *syn-* meaning together with, in company with, and *idios* meaning singular, distinct, separate

emotional contact, rather than by virtue of it. There are certain minor traits in general behavior which are sometimes quite characteristic. Syntropic individuals tend to be "free and easy" in social intercourse, even in actual bodily contacts, for instance walking arm-in-arm with companions, whereas idiotropic individuals are often conscious and self-conscious of the most meaningless and inadvertent physical contacts. While it is not intended to discuss in more detail these differences in affective attitude,<sup>37</sup> an example from the pathological sphere may be given. Delusions of persecution have been distinguished, according to whether the persecution was deserved or undeserved, into delusions which are condemning (*belastend*) and delusions which are condoning (*entlastend*). There is, however, this further distinction between delusions of persecution in many cases: idiotropic individuals are often persecuted by individuals or groups which themselves, *according to the patient's point of view and evaluation*, are not socially integrated and conforming, are "different" or outlaws, or entirely individualistic and without any connection with the social scheme—for example, "the Catholics," "the Jews," "the Masons," "the political enemy," "the devil," "the underworld," or, quite indifferently, "men" or "women." Syntropic individuals, on the other hand, often elaborate delusions of persecution where the persecutors are, in the eyes of the patient, the very essence and symbol of social contact and cohesion, for example, "all the inhabitants of the home town," "the police," "all decent women," "the whole family," "all my friends," "the government," "every moral person." Practically the kernel of the group of individuals described by Jung as *intravert* and *extravert*, by Kretschmer as *schizoid* and *cycloid*, and by Hoch as *shut-in personality*, is closely related to these idiotropic and syntropic tendencies.

The formulations of the pre-psychotic personalities were made at the same time as the psychiatric diagnoses. It is often difficult to arrive at a conclusion about the pre-psychotic personality of mental patients. Frequently the information given by relatives, for example, is not reliable. It can be observed sometimes that relatives and friends have a distinct tendency, in cases of severe psychoses, to de-

<sup>37</sup> The theoretical and clinical bearing of this train of thought will be discussed in a later study.



scribe the personality as what *in their own evaluation* is as good and "normal" as possible. In mild disorders, on the other hand, they often have the tendency to make it appear to the physician as if the patient had been always somewhat abnormal, and as if there was not much change in him which necessitated his admission to the hospital. This occurrence is not unimportant in a clinical study of the pre-morbid

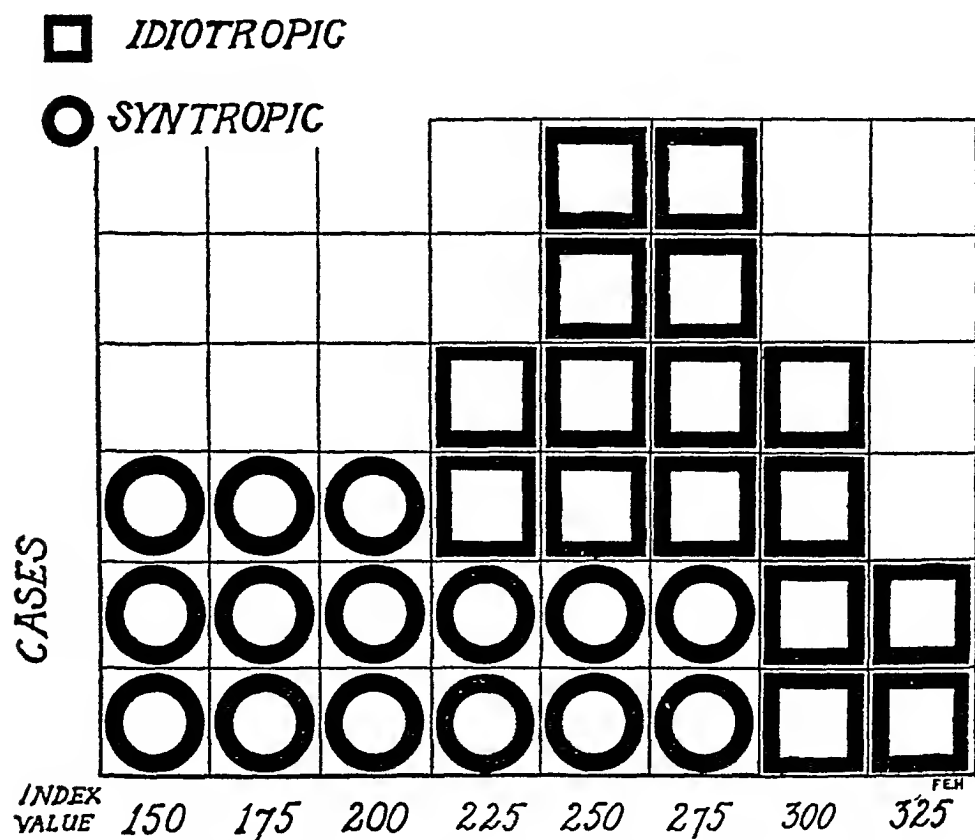


FIG 19 RELATIONSHIP BETWEEN INDEX VALUES AND PERSONALITY TENDENCIES

personality, and may be spoken of as the phenomenon of distorted personality anamnesis.

The following is an example of a summary of idiotropic tendencies (quoted from 90).

Schizophrenia of predominantly hebephrenic type, with characteristic hyposthenic bodily constitution, school-girl, aged sixteen. Pre-psychotic personality wilful child, showed little affection toward family, with abrupt

changes from one to another, did not want to be touched or kissed, contrary, reserved, had few contacts with boys or girls, daydreamer Had crushes on girls and on an older man with whom she had never spoken Feeling of inferiority, learned well, but did not retain well Aspired to be either "athletic" or "intellectual," not as clever as sisters On basis of inferiority feeling, was selfish, bluffing, gave the appearance of conceit

Only 31 patients could be assigned to the idiotropic or syntropic groups, either because there was not enough reliable information or because a predominance of idiotropic or syntropic tendencies did not clearly exist

The correlations between index values and syntropic and idiotropic tendencies can be seen on figure 19

The average index of the syntropic group is

$$217.2 \text{ (153-291)}$$

The average index of the idiotropic group is

$$289.4 \text{ (242-337)}$$

The following are the percentages of body types derived from observation in the syntropic and idiotropic groups

#### *Syntropic*

	<i>per cent</i>	
Pyknic	53.4	
Pyknoid	33.3	
Asthenic	6.65	} 13.3
Athletic	6.65	

#### *Idiotropic*

Pyknic	0	
Pyknoid	18.7	
Asthenic	18.7	} 74.9
Athletic	18.7	
Asthenic athletic mixed	37.5	
Unclear	6.3	

It will be seen that in the syntropic group pyknic forms predominate over the asthenic and athletic types There are no dysplastic traits occurring in this group The opposite is true of the idiotropic cases

The correlations between body-type and personality tendencies seem to be somewhat more pronounced than those with psychoses This may be due to some extent to the possibility that by this selection



FIG 20 MR PICKWICK

From the drawing "A Coaching Dream of Dickens" by Houghton, illustrating the pyknic habitus in a syntropic personality (Compare description of pyknic habitus, page 394 )

of distinct pre-psychotic personality patterns the more constitutional psychotic reactions were selected. On the other hand it must be realized that from the description of the personality alone, from which the personality diagnoses were made, it can not be said whether or not any of the individuals would later develop a psychosis. That these personality differences exist, and that they may have biological correlations with bodily habitus is very likely. One is reminded of the physical habitus of certain characters in history and fiction, like Mr Pickwick, the benevolent, genial founder of the Pickwick Club in Dickens' novel (fig 20), in contrast to the erratic, always isolated Don Quixote, in Cervantes' novel, whose slender body-type is traditional in all pictorial representations.

#### CONCLUSION, ASPECTS OF THE HUMAN CONSTITUTION

It seems justified to assume that there is a certain correlation between morphological constitution, mental disease and personality. The broader forms of habitus seem to occur more frequently in affective psychoses and syntropic personalities, the more slender body forms in schizophrenic psychoses and idiotropic personalities. Dysplastic traits seem to have an affinity for schizophrenic reactions. A numerical formula for this relationship can not yet be attempted with any degree of exactness. It is tempting to venture upon the genetic interpretation of these types. The dysplastic traits described are undoubtedly similar to certain endocrinological disorders, particularly of the gonads and the pituitary. The morphological and mental changes in cretinistic degeneration and myxoedema, which in the latter through thyroid medication are said to have led to perhaps the most sensational therapeutic successes in the whole field of medicine, are an often-quoted example of endocrine etiology. Only the experiment can show how far this analogy can be carried through. In the psychopathological sphere, the polymorphous picture of the psychopathological conditions due to and influenced by hyperthyroidism and dysthyroidism<sup>33</sup> shows the danger of generalizations. The metabolic disorders and the disturbances of the vegetative nervous system described

<sup>33</sup> See Wertheimer and Lyman (92). The hallucinatory psychosis with fear and confusion (case 7) was operated upon and finally took a chronic more or less typical schizophrenic course.

in affective and in schizophrenic psychoses may well be more directly related to the morphological constitution as a whole than to the psychopathological reaction itself

The problem of morphological changes in endocrine disorders has not been approached with sufficiently accurate 'anthropometric methods'. Instead, impressionistic morphological traits were translated into a highly speculative endocrinological language. The same holds true of the endocrinological interpretation of psychological types, L. Berman's recent book "The glands regulating personality" is an example. Even in the relatively simple sphere of eunuchoid personalities, no unitary decision has been reached. Frankel (22) finds in the eunuchoid character the most multiform qualities. Scherk (78) finds among eunuchoids a "unitary mental structure" which can be clearly defined and delimited as a whole, and shows variations only as to degree—in other words, a psychological "type". Kretschmer (46) sees close analogies between eunuchoids and schizoid psychopathic personalities. It is evidently for such reasons that Lipschutz (51) says "The deeper one enters into the problem of connections between inner secretions and personality, the clearer it becomes that every progress in this special question is dependent on a more thorough study of the typological problem itself" (p. 253).

A fundamental connection between body architecture and mental disease, or disposition to mental disease, is inconceivable unless one would believe in a fate-like transmission of both. A genetic explanation would have to take into account constitutional signs in the physiological sphere. The possible variations of simple physiological activities in different individuals have received very little scientific attention. According to Wuth (93) the carbohydrate tolerance, endogenic purin and creatinin excretion, and nitrogen minimum show a remarkable individual constancy and may well have correlations with other constitutional signs. From the facts that have been definitely established it seems, however, more than likely that the individual variations of even the most simple physiological reactions like the knee-jerk or the respiration volume, are far greater than the variation of certain morphological signs. Rautmann (71) has obtained from soldiers and students data which show this for a number of

morphological and physiological signs. The smaller the range of individual variations for one sign, the greater significance may be attached to it, if it shows in an individual or a group of individuals values outside the usual small range of variations. Apart from their great variability, however, the correlations of physiological reactions among themselves are as yet very uncertain, even in the field of the vegetative nervous system, which seemed to offer most hopes for the establishment of physiological types. From the physiology of respiration Rutz (1911) (quoted by Grubic (27)) has distinguished four respiration types, with supposedly characteristic mental make-up

- 1 The abdominal type
- 2 The ascending type
- 3 The descending type
- 4 The thoracic type

but although his observations are doubtless interesting, these types are somewhat speculative and construed.

The concept of the unity of the organism has been used in recent times by biologists and psychiatrists. Yet in the field of investigation of the human constitution the limitation of methods makes desirable the distinction of the morphological, physiological or psychological aspect of constitution. No attempt to explain the human organism as a whole can be complete which leaves out any one of them. Attempts have been made very frequently to make short-cuts and to express psychological reactions in terms of morphology or physiology. Graves (26), one of the last scientists imbued with the spirit of Gall, has taken refuge with the shoulder-blade for the estimation of human adaptability, because he wrongly believes that "we cannot subject the mental side of man to direct observation." The uselessness and danger of translating psychological facts immediately into a physiological language "which at present is entirely arbitrary" (36) has been often pointed out, especially by Janet and Adolf Meyer. The modern psychoanalytic mechanism of compensation has been directly related by Lewis (49) to "somatic compensatory changes of growth" in paranoid schizophrenic patients. The constitutional types of Kretschmer have already led with some authors to a terminology in which morphological and psychiatric expressions are mixed. Liepmann (50)

contrasts the "pyknic" type with the "schizoid" type (p 168) In a similar way Naccarati (63) on page 256 states that Kretschmer's "pyknic types" correspond to the macrosplanchnic, the "schizoid types" to the microsplanchnic, or, in another place (62), "Too much mental repression and the quick muscular exhaustion make the hyperthyroid a prospective candidate for the asthenic forms of psychoneurosis" This latter passage illustrates well the mixture of psychodynamic, physiological, endocrinological and psychiatric-clinical language. Pende (65) has elaborated a speculative simplified scheme in which he reduces "morpho-physiological" and psychological facts to two biotypes (p 48).

Although we must assume that structure and function have a definite relationship also in the sphere of psychobiological integration, both the extent and the nature of this relationship are as yet unknown and a field for investigation To use morphological constitutional signs for psychiatric diagnosis or prognosis is premature, although the incidence of dysplastic features may perhaps be used with some caution in differential diagnosis Nevertheless, the possibility of morphological and psychopathological correlations opens a field for investigation with a bearing upon many lines, and seems to have a significance which no thoughtful clinician can overlook.

#### SUMMARY

1 From a historical study of the subject of characteristic body types it becomes clear that:

*a.* Attempts to describe body types have been made frequently, the early studies were mixtures of morphological, physiological and psychological features

*b.* Medical studies of the subject were undertaken primarily with the view of correlating body types with disposition to disease as in de Giovanni's investigations.

*c.* In psychiatry anthropological studies were influenced largely by the doctrine of degeneracy (Morel, Lombroso).

*d.* A comparison of attempts to formulate morphological types shows a remarkable uniformity of the characteristic body forms aimed at by different investigators These various classifications have not all been

collected and compared before, some authors having been overlooked in the literature on the subject, and almost forgotten (Carus, de Giovanni, Mills, etc.)

2 For the purpose of investigations like the present one, the human constitution is defined as the correlative unity of those morphological, physiological and psychobiological developments of the individual which are definitely more influenced by heredity than by environment

3 From a critical review of the methods to be applied it becomes apparent that methods of observation and exact measurements have to be used, the problems of clinical anthropology are different from those of racial anthropology, and therefore the methods have to be adapted accordingly

4 The descriptions of types given by Kretschmer are the most useful. Very similar types have been described before by other authors (de Giovanni, Manouvrier, etc.) Drawings of two young individuals of the same age are given here as illustrations of the main differences between the pyknic and asthenic types (Plates I-V)

5 The methods of observation are clarified and simplified by the introduction of schematic diagrams, showing typical forms of trunk profile, head outline, hands, forehead, lips and chin (Figs 3-7)

6 From an inductive study using exact anthropometric measurements alone no morphological types were found

7 A critical review of so-called constitutional indices shows that none of them can be put to clinical use, for example, the Pignet Index used by Henckel contains weight, which is variable in mental disease

8 A new index using skeletal points alone is described

$$\text{Index} = \frac{\text{Leg length} \times 10^3}{(\text{Transverse chest } D^*) \times (\text{sagittal chest } D) \times (\text{trunk height})} \times 100$$

\* *D* represents diameter

This index is based on de Giovanni's conception that the impression of the existence of morphological types is based on the relation of trunk volume to limb length. In the 65 patients of this study the observation types agree remarkably with the index values, showing that the extreme low index values correspond to the pyknic type and the extreme high values to the asthenic type, with the less characteristic



types between In this way it is shown for the first time with exact anthropometric methods that there are no types in the strict sense, but only transitions which probably fit into a normal frequency curve, the extreme forms impressing one as types

9 The clear asthenic, athletic and pyknic observation types of Kretschmer can be exactly differentiated by the use of the index; the athletic type stands between the asthenic and pyknic types, according to the index, but definitely nearer the asthenic

10. The practical advantage of the index is that it can easily be put to clinical use.

11. The influence of race and occupation on these typical body forms seems negligible

12 Among the patients with high index values the schizophrenic psychoses predominate over the manic-depressive psychoses, among the patients with low index values (pyknic and pyknoid) the manic-depressive psychoses predominate The exact numerical relationship cannot yet be established on account of the influence of age and growth

13 Cases in the affective group specified as showing schizophrenic reactions show morphological characteristics which are more frequent in the schizophrenic group

14 Dysplastic features (anomalies in the distribution of hair and fat, marked disproportions of the body) predominate very definitely in the schizophrenic group, so that with some caution they may be used in differential diagnosis

15. The age displacement of types is an important source of error (less significant for dysplastic features), with the percentages of body types in psychoses given by Kretschmer and other investigators using his methods, one is forced to consider that the average age of unselected manic-depressive patients is greater than that of schizophrenic patients Kretschmer quotes Rohden: in 937 manic-depressive cases 66 per cent are pyknic, in our group of patients the percentage is only 45.5 per cent If, however, the cases under thirty years of age are left out, the percentage is 66.6 per cent

16 Two groups of prepsychotic personalities are contrasted with regard to the affective attitude toward the personal and social environment, those who seek satisfaction in emotional contact with others

(syntropic) and those who find satisfaction in being detached and isolated, with the emphasis of their emotional experiences not on other personalities but more on the reactions and ramifications of their own mental experiences both intellectual and imaginative (idiotropic). These characteristics do not constitute personality types, but denote antagonistic directive tendencies with regard to affective attitude.

Average index of syntropic group	217.2
Average index of idiotropic group	289.4

The pyknic habitus predominates in the syntropic group, the asthenic-athletic types in the idiotropic group.

17. The endocrinological interpretations of morphological and psychological types are speculative (Pende, Berman, Naccarati, etc.), a genetic explanation of the relationship between morphology and psychopathology will, however, have to take into account constitutional signs in the physiological sphere. The limitation of methods makes desirable the distinction of the morphological, physiological and psychological aspects of the human constitution.

#### BIBLIOGRAPHY

- (1) ADAM, L. *Buddhastatuen. Ursprung und Formen der Buddhagestalt.* Stuttgart, 1925.
- (2) ASCHNER, B. *Die Konstitution der Frau und ihre Beziehungen zur Geburtshilfe und Gynäkologie.* München, 1924.
- (3) BACH, F. *Körperbaustudien an Berufsringern.* *Anthropologischer Anzeiger*, 1924, 1, 200.
- (4) BARRETT, C. R. *The height weight index of build in relation to linear and volumetric proportions and surface-area of the body during post natal development.* Carnegie Institute of Washington, Publ. 272.
- (5) BAUER, J. *Konstitutionelle Disposition zu inneren Krankheiten.* 3rd ed., Berlin, 1924.
- (6) BAUER, J. *Phänomenologie und Systematik der Konstitution und deren dispositionelle Bedeutung auf somatischem Gebiet.* *Handbuch der normalen und pathologischen Physiologie*, Berlin, 1926, vii.
- (7) BEAN, R. B. *The two European types.* *Am Jour Anat.*, 1923, xxxi, 359.
- (8) BERINGER AND DÜSER. *Über Schizophrenie und Körperbau.* *Ztschr. f. d. ges. Neurol. u. Psychiatr.*, 1921, lvi, 12.
- (9) BORCHARDT, L. *Die vegetativen und die somatischen Funktionsänderungen der Organe als Ursache von Konstitutionsanomalien.* *Medizinische Klinik*, 1925, xxi, 1347.
- (10) BORCHARDT, L. *Die Anthropometrie im Dienste der klinischen Konstitutionsforschung.* *Deutsche med. Wchnschr.*, 1924, i, 1318.

- (11) BRUGSCH, T. Allgemeine Prognostik oder die Lehre von der arztlichen Beurteilung des gesunden und kranken Menschen Berlin u Wien, 1918
- (12) BRYANT, J The carnivorous and herbivorous types of man Boston Med and Surg Jour, 1916, clxxiv, 412
- (13) CARUS, C. G Symbolik der menschlichen Gestalt Celle, 1925 (1st ed, 1853)
- (14) COOMARASWAMY, ANANDA Buddha and the Gospel of Buddhism Iconography, p 330, New York, 1916
- (15) DAVENPORT, C B Body-build and its inheritance Carnegie Instit Washington Publ 329, paper 35, 1923
- (16) DUBREUIL-CHAMBARDEL, L Les variations du corps humain, Paris, 1925
- (17) ESQUIROL Folie Dictionaire des sciences médicales, Paris, 1816, xvi
- (18) FISCHER, E Anthropologie, Kultur der Gegenwart Leipzig u Berlin, 1923, Teil iii, Abt. v
- (19) FISCHER, H Zur Biologie der Degenerationszeichen und der Charakterforschung Ztschr f d ges Neurol u Psychiatr, 1920, lxi, 261
- (20) FISCHER, H, AND HOFFMANN, H Ein Beitrag zur Körperbauforschung Innersekretorische Faktoren in der Genese der Körperproportionen von der Pubertät bis zum Reifungsabschluss Monatschr f Psychiatr u Neurol, 1924, lvi, 153
- (21) FLORSCHUTZ, G. Allgemeine Versicherungsmedizin Berlin, 1914
- (22) FRANKEL, F. Der psychopathologische Formenreichtum der Eunuchoiden Ztschr f d ges Neurol. u Psychiatr, 1923, lxxx
- (23) GIBBS, C E Sex development and behavior in male patients with Dementia Praecox. Archiv Neurol u Psychiatr, 1923, ix, 73
- (24) DE GIOVANNI, ACHILLE Clinical commentaries deduced from the morphology of the human body. Transl from the 2nd Italian ed by J J Eyre, New York, no date (1910?).
- (25) GOULD\* quoted by Aschner (2)
- (26) GRAVES, W W. The relations of shoulder blade types to problems of mental and physical adaptability Lecture IV under the Henderson Trust, Edinburgh, 1925.
- (27) GRUHLE, H. W. Historische Bemerkungen zum Problem Charakter und Körperbau Ztschr f d ges Neurol u Psychiatr, 1923, lxxxiv, 444
- (28) GUNTHER, H Die Grundlagen der biologischen Konstitutionslehre Leipzig, 1922
- (29) HADDON, A C History of Anthropology London, 1910
- (29a) HALLÉ ET THILLAYE Tempéramens Dictionaire des sciences médicales, Paris, 1821, lv
- (30) HENCKEL, K O Körperbaustudien an Geisteskranken II Der Habitus der Zirkulären Ztschr f d ges Neurol u Psychiatr, 1924, xcii, 614
- (31) HENCKEL, K O Körperbaustudien an Schizophrenen Ztschr f d ges Neurol u Psychiatr, 1924, lxxxix, 82
- (32) HERING, A E Über den funktionellen Begriff Disposition und den morphologischen Begriff Konstitution vom medizinischen Standpunkt aus Münch med Wchnschr, 1922, lxi, 691
- (33) HIRT, E Wandlungen und Gegensätze in der Lehre von den nervösen und psychotischen Zuständen Würzburg, 1914
- (34) HRDLÍČKA, A Anthropometry Philadelphia, 1925
- (35) HRDLÍČKA, A A few points about anthropometry American Jour of Insanity, 1896-1897, lmi, 521
- (36) JANET, P Principles of psychotherapy New York, 1924

- (37) KAHN, E. Über Ehepaare mit affektiven Psychosen und ihre Kinder. *Ztschr f d ges Neurol u Psychiatr*, 1926, ci, 248
- (38) KAHN, E. Erbbiologische Einleitung. Aschaffenburg, G. *Handbuch d. Psychiatrie*, 1925, Abt 1, Teil 3
- (39) KEHRER, F., AND KRETSCHMER, E. Die Veranlagung zu seelischen Störungen. Berlin, 1924
- (40) KERN, H. Die Charakterologie des Carl Gustav Carus. *Jahrbuch der Charakterologie*, 1926, ii-iii, 45
- (41) KOLLE, K. Der Körperbau der Schizophrenen. *Archiv f Psychiatr*, 1925, lxxii, 40
- (42) KOLLE, K. Körperbaustudien an Zirkulären. *Zentralbl f d ges Neurol u Psychiatr*, 1926, xlii, 605
- (43) KRETSCHMER, E. Die Anthropologie und ihre Anwendung auf die ärztliche Praxis. *Münch med Wchnschr*, 1922, lxx, 121
- (44) KRETSCHMER, E. *Physique and Character*. Eng Transl, New York, 1925
- (45) KRETSCHMER, E. Lebensalter und Umwelt in ihrer Wirkung auf den Konstitutionstypus. *Ztschr f d ges Neurol u Psychiatr*, 1926, ci, 278
- (46) KRETSCHMER, E. Zur Psychopathologie der Keimdrüsenstörungen. *Zentralbl f d ges Neurol u Psychiatr*, 1921, xxv, 342
- (47) KRAEPELIN, E. *Psychiatrie*. 8th ed., 1923, iii, 1229
- (48) KUNDRAT, H. Über Vegetationsstörungen. *Wien Klin Wchnschr*, 1893, vi, 505
- (49) LEWIS, N. D. C. The constitutional factors in Dementia Praecox. *Nervous and Mental Dis Monograph Series*, 1924, No 35
- (50) LIEPMANN, W. *Gynäkologische Psychotherapie*. Berlin u Wien, 1924
- (51) LIPSCHÜTZ, A. Innere Sekretion und Persönlichkeit. *Jahrbuch der Charakterologie*, 1926, ii-iii, 228
- (52) LUDOSCH, W. *Grundriss der wissenschaftlichen Anatomie*. Leipzig 1925
- (52a) MACAULIFFE, I. Les origines de la morphologie humaine, *Bull de la Soc d'Étude des Formes Humaines*, 1925, No 2 and 3, 155
- (53) MALLA, KALYANA Ananga Ranga. Transl from the Sanskrit by T. F. Arbuthnot and R. F. Burton, Paris, 1907
- (54) MANOUVRIER, L. Étude sur les rapports anthropométriques en général, et sur les principales proportions du corps. *Mém de la Soc d'Anth de Paris*, 1902, Ser iii, T ii
- (55) MARTIN, R. *Anthropometrie*. Berlin, 1925
- (56) MARTIN, R. *Lehrbuch der Anthropologie*. Jena, 1914
- (57) MAYER-GROSS, W. Kretschmer's Körperbaulehre und die Anthropologie. *Münch med Wchnschr*, 1922, lxx, 676
- (58) MEYER, ADOLF. An attempt at analysis of the neurotic constitution. *Amer Jour of Psychol*, 1903, xiv, 90
- (59) MILLS, R. W. The relation of bodily habitus to visceral form, position, tonus and motility. *Amer Jour of Roentgenology*, 1917, ii, 155
- (60) MÜLLENSTOFF, F. Zur Frage der Beziehungen zwischen Körperbau und Psychose. *Archiv f Psychiatr u Nervenkrankh*, 1924 lxxii, 98
- (61) MOPF, B. A. *Traité des dégénérescences physiques, intellectuelles et morales de l'espèce humaine et des causes qui produisent ces variétés malades*. Paris 1857
- (62) NACCARATI, S. The morphologic aspect of intelligence. *Archiv Psychol*, 1921, xlv

- (63) NACCARATI, S, AND GARRETT, H E The relation of morphology to temperament. *Jour Abnorm and Soc Psychol*, 1924-1925, xix, 254
- (64) NASSE (1859) Quoted by Rosenfeld, M Über den Einfluss psychischer Vorgänge auf den Stoffwechsel Allgemein *Ztschr f Psychiatr*, 1906, lxii, 367
- (65) PENDE, N Konstitution und innere Sekretion *Abhandlungen aus den Grenzgebieten der inneren Sekretion* Budapest and Leipzig, 1924
- (66) PERDULCIS BARTHOLOMAEI De morbis animi liber Paris, 1639
- (67) PETERSON, F Craniometry and cephalometry in relation to idiocy and imbecility *Amer Jour of Insan*, 1895-1896, lii, 73
- (68) PIGNET Du coefficient de robusticité *Le Bulletin Médical*, Paris, 1901, xv, No 33
- (69) POLLACK, H M Personal communication quoted by F I Wertheimer A brief survey of American Psychiatry *State Hospital Quarterly*, 1926, xi, 167
- (70) PRITCHARD, J C A treatise on insanity and other disorders affecting the mind Phila, 1837
- (71) RAUTMANN, H Klinische Variationsforschung *Klin Wchnschr*, 1926, v, 493
- (72) REICHARDT, M Allgemeine und spezielle Psychiatrie Jena, 1918
- (73) REICHARDT, M Die Anlageforschung in der Psychiatrie und die sog physikalische Hirnuntersuchung *Ztschr f d ges Neurol u Psychiatr*, 1923, lxxxiv, 561
- (73a) ROSTAN, L Cours élémentaire d'hygiène, 2e ed, 2 vols, Paris, 1828
- (74) VON ROHDEN, F Über Beziehungen zwischen Konstitution und Rasse *Ztschr f d ges Neurol u Psychiatr*, 1925, xcvi, 255
- (75) SCHEIDT, W Allgemeine Rassenkunde München, 1925
- (76) SCHEIDT, W Anthropometrie und Medizin *Munch med Wchnschr*, 1921, lxxvii, 1653
- (77) SCHEIDT, W Somatoskopische und somatometrische Untersuchungen an Knaben des Pubescenzalters *Ztschr f Kinderforsch*, 1923, xxviii, 71
- (78) SCHERK, G Zur Psychologie der Eunuchoiden *Kleine Schriften zur Seelenforschung*, Stuttgart, 1924
- (79) SCHULTZ, A H Anthropological studies on Nicaraguan Indians *Amer Jour of Physical Anthropology*, 1926, ix, 65
- (80) SHAW, F C A morphologic study of the functional psychoses *State Hospital Quarterly*, 1925, x, 413
- (81) STAHL, G E De venae portae porta malorum hypochondriaco-splenitico-suffocativo-hysterico-haemorrhoidanorum Halle, 1698 (Quoted by Laehr, H - Gedenktage der Psychiatrie Berlin, 1893)
- (82) STERN Kulturkreis und Form der geistigen Erkrankung Halle, 1913 (Quoted by Mollenhoff (60))
- (83) STERN-PIPER, L Kretschmer's psycho-physische Typen und die Rassenformen in Deutschland *Archiv f Psychiatr u Nervenkrankh*, 1923, lxxvii, 569
- (84) STILLER, B Die asthenische Konstitutionskrankheit Stuttgart, 1907
- (85) STOCKARD, C R Human types and growth reactions *Amer Jour Anat*, 1923, xxxi, 261
- (86) SULLIVAN, L R Essentials of Anthropology New York, 1923
- (87) TAGORE, A N Art et anatomie hindous Paris, 1921
- (88) VATSYAYANA Kamasutram Transl from the Sanskrit by R Schmidt, Berlin, 1915
- (89) VON VERSCHNER, O Die Wirkung der Umwelt auf die anthropologischen Merkmale nach Untersuchungen an eineigen Zwillingen *Archiv f Rassen- u Gesellschafts-Biologie*, 1925, xvii, 149.

- (90) WALKER, A. Analysis and classification of beauty in woman. London, 1852  
(Quoted by Stratz, C H. Die Schönheit des weiblichen Körpers. Stuttgart, 1922)
- (91) WALTER, F K. Die materiellen Grundlagen der geistigen Persönlichkeit. Jahrbuch der Charakterologie, 1924, 1, 353
- (92) WERTHEIMER, F I, AND LYMAN, R S. Clinical demonstrations of mental disorders from the point of view of psychopathology and internal medicine. Mental Hygiene, 1925, 11, 360
- (92a) WERTHEIMER, F I. Les Rapports de la Morphologie humaine avec les Types Psychopathiques. Annales Médico-Psychologiques, lxxxiv, 1926
- (93) WUTH, O. Konstitution und endokrines System. Münch med Wchnschr, 1922, vi, 392
- (94) ZERNER, H. Beiträge zur Kenntnis der durch Abstammung und Entwicklung bedingten körperlichen Schwächeanomalien. Sammlung klinischer Vorträge, Leipzig, 1912, 667-668
- (95) ZWEIF, H. Habitus und Lebensalter. Ztschr f angew Anatomie u, Konstitutionslehre, 1919, iv, 255

PLATE 1

MANIC-DEPRESSIVE PSYCHOSIS, DEPRESSIVE PHASE SYNTROPIC PERSONALITY AGE  
TWENTY-THREE PYKNIC HABITUS INDEX 246

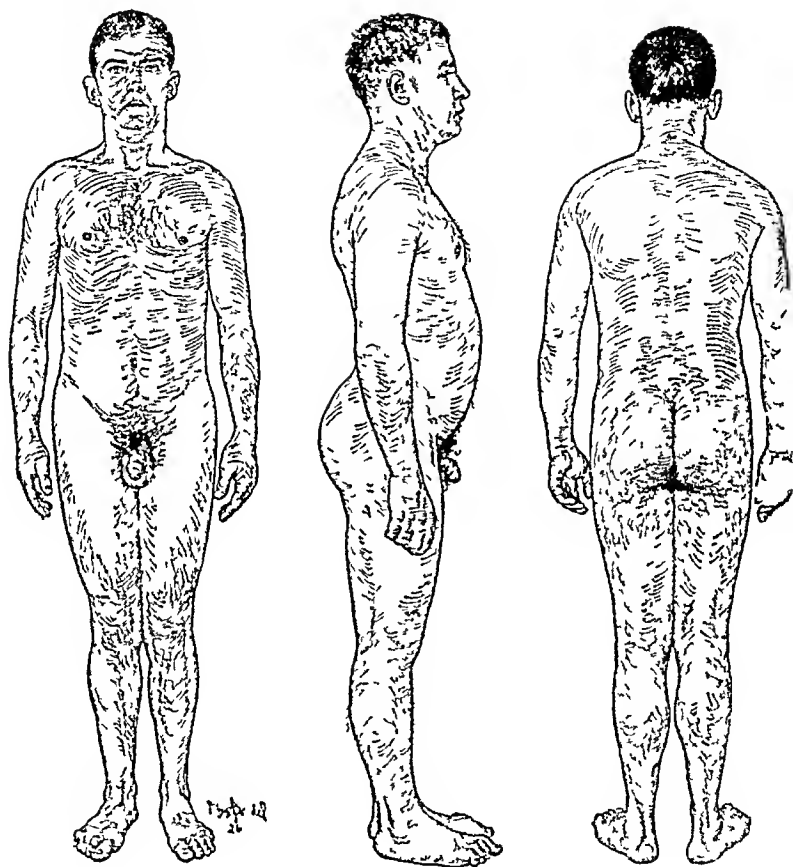
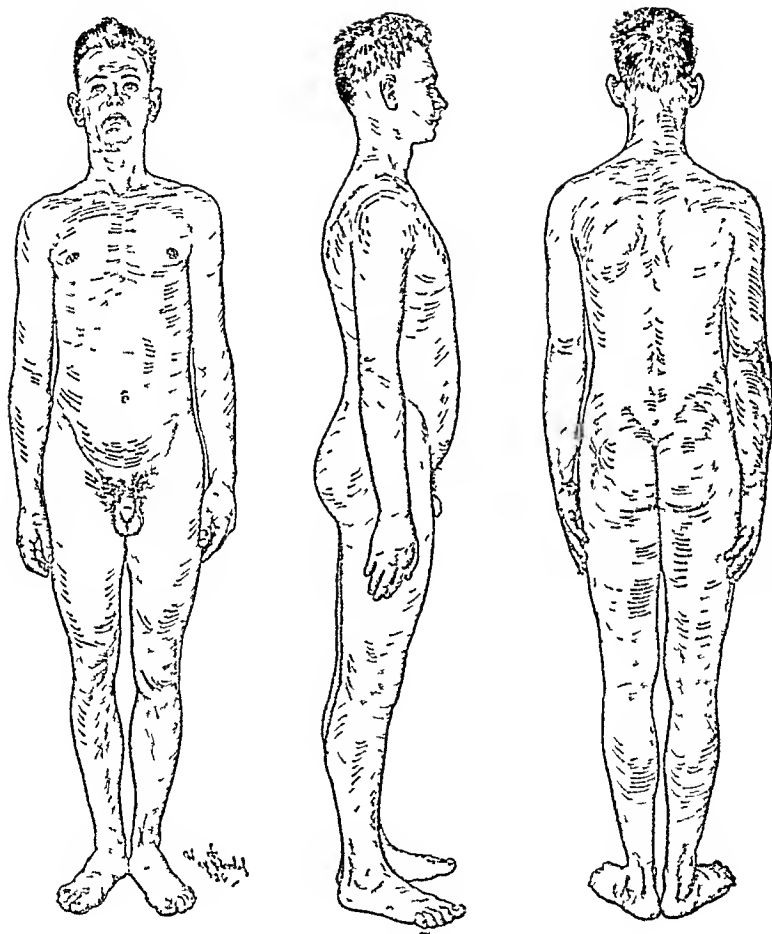




PLATE 2

HYPPOCHONDRIASIS IN SCHIZOID (IDIOTROPIC) PERSONALITY AGE TWENTY-THREE,  
ASTHENIC HABITUS INDEX 305



(Worth and Hewach. Physical emaciation in mental disease)

auto-infection which patients with hard chancres exhibited, was well developed before the appearance of generalised lesions. Indeed, so firmly was the principle established that wide-spread use was made of it in the differential diagnosis between chancre and chancroid. Thus it came about that before the year 1865 literally thousands of purposeful reinoculation experiments had been performed upon syphilitic individuals in the early stages of their infection.

Rollet has summarized all this work and his conclusions are of interest for they give us an accurate idea of the then-existing (1865) state of knowledge concerning this subject. Says Rollet,

If reinoculation is possible before the appearance of syphilis, when it is in the stage of incubation, it is no longer so at the time when the primary lesion appears: when the chancre is manifest, when it commences to develop, it is irremoculable, and it preserves this same character of irremoculability during the entire period of its evolution (experiments of Nodet).

From that time on immunity is an accomplished fact. One finds it in secondary syphilis to the same extent as in primary syphilis, it is also found in tertiary syphilis and even in old syphilitics several years after the disappearance of every lesion (experiments of Baerensprung). That is the general rule. As for the exceptions, however rare they may be, they show us that in some cases, in the primary as well as in the secondary stage of the disease, this immunity cannot be absolute. Reinoculations have been made with success, but in a very small number of cases, and the result, which, in order to be complete, should have reproduced the regular course of the disease, has always been but slightly pronounced.<sup>3</sup>

Thus matters stood in 1866 and for some time thereafter, as evidenced by the summary of the situation by Mauriac, (16) who in 1883 wrote as follows

1 Reinoculation is possible before the appearance of the chancre and during the first incubation, at least up to the twenty-second day of this period

2 It is no longer possible when the chancre begins to develop

3 During the entire evolution of the chancre the immunity is an accomplished fact ("un fait accompli")

<sup>3</sup> Writer's translation

4 This immunity persists in the secondary period to the same extent as in the primary period

5 One finds it also in tertiary syphilis and even in old syphilitic patients many years after the disappearance of every manifest lesion

6 In very exceptional instances reinoculations have been made with success, but without the characteristic adenopathies or the cutaneous, mucous or other lesions which always accompany the true syphilitic chancre

7 The immunity, which *a priori* one would think ought to diminish with time, appears actually from experimentation (observation of Schnepf) to be less than during the secondary period

8 A syphilitic individual would be more apt to be refractory to his own virus than to the virus from an individual who had attained a more advanced and perhaps more intense stage of the disease

9 In general the pretended reinoculations are very hypothetical and in the experiments immunity has always been the rule in all stages of syphilis

To all of these propositions, except number 8, Neisser gives his assent

Even before Mauriac wrote the foregoing, instances were being reported in which persons with chancres had been successfully inoculated a second time and a syphilitic lesion produced. In general, however, in the case of these apparent exceptions to the rule reinoculation was performed soon after the appearance of the chancre and not during the latter part of the primary period. When reinoculation was performed later it was almost uniformly negative. Although Taylor (17) was successful in producing a second chancre by inoculating with the patient's own virus as late as the 14th day after the appearance of the original lesion and Pontoppidan (18) produced lesions by inoculating a patient 17 days after the appearance of the chancre, the number of successful reinoculations during this period of the disease was far below the number of failures. There seems to be general agreement that the lesions produced by auto-inoculation were not as characteristic as the original chancre.

These older experiments, granting the clinical diagnosis was correct, showed that the refractory state is not present in man before the appearance of the chancre but is manifest shortly after the primary lesion is established. Toward the end of the primary stage and during

the period of manifest secondary lesions the refractory stage is practically complete and universal, according to the older work

It is difficult to form an opinion from the older literature as to the susceptibility of patients with late syphilitic lesions to a new infection, because there are so few observations or experiments on record. Occasional instances of reinfection in patients known to have had syphilis previously have been reported but the authenticity of these has been criticised. Auto-inoculations upon the bearers of tertiary lesions proved negative. Schnepf (19) in one instance apparently succeeded in reinfecting a syphilitic individual showing numerous gummata with virus from another patient. The most that can be said in this respect is that there are on record in the older literature a very small number of observations which indicate that in exceptional instances a person infected with syphilis several years previously may acquire a second infection. These cases must be regarded as constituting exceptions to, rather than examples of a general rule.

Even if one were inclined to dismiss all the evidence for the existence of acquired immunity in syphilis accumulated by the clinical investigators of the last century, on the grounds that accurate diagnosis was impossible through lack of knowledge of the causal agent of the disease, one would not be justified in dismissing the evidence obtained by purposeful inoculations performed upon syphilitic human beings in the years following the discovery of the *Treponema pallidum*, any more than one can dismiss the information obtained from study of the experimental disease in the lower animals. The era following the recognition of the causal agent of the disease and the successful reproduction of the infection in animals has indeed proved to be a most fruitful one and the facts acquired during that time have contributed enormously to our knowledge of the subject. We shall approach this phase of the work by considering what takes place in human beings, monkeys and rabbits at different periods, more or less arbitrarily chosen, in the course of the infection.

*1 Incubation period. a. Man.* The writer has been unable to find any account of experiments performed since 1905 upon human beings during the first incubation period before the appearance of the primary lesion, although there were a few such experiments in the preceding century.

*b Monkeys* Metschnikoff and Roux (20) succeeded in producing lesions in an orang-outang with a second inoculation performed 10 days after the first inoculation, which also resulted in the production of a lesion. The incubation period of the second lesion was shorter than that of the first by 6 days. Finger and Landsteiner (21) in 5 experiments upon rhesus monkeys succeeded in each instance in producing second infections when the second inoculation was performed 9 to 14 days after the first. The average incubation period of the second chancre was 7 days shorter than that of the first. Similar results were obtained by Neisser in 9 apes when the second inoculation was made during the first incubation period, even if an interval as long as 51 days elapsed between the first and second inoculations. The incubation period of the second lesion was not always shorter than that of the first. Kraus and Volk (22) also succeeded in producing superinfections in apes by inoculating a second time as late as 23 days after the first inoculation and before the first chancre had appeared. They did not always find a shorter incubation period for the second chancre but did note that such lesions were not typical and tended to be smaller and to heal more rapidly than those produced by the first inoculation.

*c Rabbits* Truffi (23) found that second infections could be produced with considerable regularity in rabbits if inoculation were performed during the first incubation period and Nichols (24) stated that "rabbits can be infected in both testicles if inoculated at the same time or within one to two weeks of each other."

Thus the experimental work on apes and rabbits supports the older clinical experiments in that it shows that during the first incubation period, up to the time of the appearance of the chancre, the host is still susceptible to a second infection introduced by scarification of the skin, and can be made to develop a second chancre. There is some indication, from the shortening of the incubation period of the second lesion in some experiments, that the host is already developing a partial resistance against foreign virus.

*2 Period of early lesions* By this term is understood the period elapsing between the appearance of the chancre and the healing of the secondary lesions. As is well known this is the period during which the maximum dissemination of organisms is taking place. It also

includes the interval during which the body manifests its first defensive reaction toward the invaders, as exhibited in the spontaneous healing of lesions. While the actual time limits of the period are perhaps better appreciated in man, they are of course not sharply defined but for purposes of discussion this period of the infection may be singled out from the others. It is far less easy to delimit it in the lower animals, however, because of the relative scarcity of secondary lesions. For that reason when we come to discuss what takes place in monkeys and rabbits we shall have to rely upon time intervals expressed in days after inoculation and chosen somewhat arbitrarily.

*a Man* That the syphilitic individual during this period of his infection gradually acquires a resistance to his own or foreign virus inoculated upon the scarified skin has been clearly demonstrated by the experiments of Queyrat, and by Levaditi and his co-workers.

Queyrat (25) conducted a series of 19 auto-inoculations by scarification of the skin of patients presenting chancres and obtained 10 positive results. Control scarifications with sterile instruments were performed in each instance. No lesions were produced if the original chancre was older than 15 days. The average incubation period of these auto-inoculation products was about 13 days. The lesions which he produced contained numerous spirochetes but he himself recognized that they did not present the typical appearance of chancres and he spoke of them as "abortive chancres." He regarded them as having been modified by the pre-existing syphilitic infection. Auto-inoculations by Nobl (25a) in 8 patients with syphilis prior to the outbreak of secondary lesions all proved negative.

Levaditi, La Roche and Yamanouchi (26) compared the results of auto-inoculation with the occurrence of the Wassermann reaction in 6 experiments upon human beings with syphilitic chancres. They succeeded in producing a second chancre in three patients with primary lesions 4 to 8 days old and in all of these the reaction was negative. In the remaining 3 patients with chancres 8-9 days old reinoculations were unsuccessful and in two of these the Wassermann reaction was positive. They attach considerable importance to this co-existence between the development of the resistant state and the development of a positive Wassermann reaction in the blood serum.

These experiments of Queyrat, of Levaditi and his co-workers and

of Nobl would indicate that a high degree of resistance of the skin toward a second syphilitic infection develops in man soon after the appearance of the primary lesion. The observations of Finger and Landsteiner and of Ehrmann upon patients with secondary syphilis would however indicate that this resistance is not absolute.

Finger and Landsteiner (27) found that if they introduced relatively large amounts of syphilitic virus into pockets made in the deeper layers of the skin of patients with manifest secondary cutaneous lesions, they were able to produce lesions which did not present the clinical characteristics of a chancre but closely simulated the lesions which the patient himself was exhibiting at the time. Control inoculations with non-syphilitic material or with heat-killed syphilitic virus were negative. In their hands these inoculations were more successful when performed before the appearance of secondary lesions than when carried out later. Thus in 27 patients inoculated in the second incubation period lesions developed in 24, or almost 90 per cent, whereas in 40 patients inoculated after the appearance of secondary lesions the number showing lesions amounted to 27, or 66 per cent.

Ehrmann (28) inoculated a series of 45 syphilitics who presented "ulcero-crustaceous papules," with material containing active syphilitic virus and obtained in each instance what he regarded as a syphilitic lesion. The lesions produced were certainly not chancres, they were described as scaly or crusted papules and were not followed by regional lymphadenitis. This series of experiments seems to have been carefully controlled to exclude the possibility of trauma alone being responsible for the production of the lesion, nevertheless Neisser criticised them and expressed considerable doubt as to whether true syphilomata were produced. The conditions under which the inoculations were carried out were such as not to exclude the possibility of secondary infection playing a rôle in the pathogenesis of the lesions. Somewhat similar but less uniform results have recently been reported by Cappelli (29).

It seems clear that characteristic primary lesions were not produced in the auto-inoculation experiments of either Ehrmann or Finger and Landsteiner. About all that one would be justified in concluding from them would be that the skin of patients with secondary syphilis is not uniformly and completely indifferent to new syphilitic virus in-



troduced under certain special conditions Zinsser is undoubtedly correct in his contention that the observations do not invalidate the conclusion that "there is a resistance at this stage higher than that of the normal subject"

*b. Monkeys.* The experimental work on monkeys has yielded results that are in strict accord with those obtained in the human experiments Metschnikoff and Roux (30) succeeded in superinfecting apes as late as 10 days after the appearance of the chancre Finger and Landsteiner in 9 experiments with rhesus monkeys succeeded in producing second infections in 6 instances when the second inoculation was made not later than 5 days after the appearance of the first chancre They noted a shortening of the incubation period of the second chancre and a diminution in the size of the lesion which they attributed to the influence exerted by the first infection Kraus and Volk succeeded in producing second chancres in syphilitic apes with primary lesions 2, 4, 6 and 11 days old but failed in 6 instances in which inoculations were made 2, 4, 5, 7, 10 and 19 days after the appearance of the first chancre They failed to note a uniform shortening of the incubation period in the case of the second infection

Neisser successfully reinoculated 2 apes on the day the original primary lesion appeared He obtained successful reinoculations in 9 apes as against unsuccessful reinoculations in 135, when the second infection was performed after the appearance of the first chancre The percentage of successful reinoculations was greatest when the attempt was made before the eightieth day of the disease, and was almost nil when the attempt was made at a later period

*c Rabbits* In the foregoing experiments upon human beings and monkeys the inoculations were almost always made by the cutaneous or subcutaneous route When we come to consider the state of affairs in rabbits we have to take into account other modes of inoculation The first authentic transmission of syphilis to the rabbit was accomplished by inoculation into the anterior chamber of the eye, with the production of keratitis In the earlier reinoculation experiments this method of inoculation was employed and it was not until later that the testicular and subscrotal methods were adopted The subcutaneous and intracutaneous methods have not been employed in rabbits to anything like the extent that they have been used in apes From the

work of several investigators it is clear that in rabbits the results obtained from reinoculation vary to some extent, depending upon the site of the original and also of the second inoculation. This point, as Tomaszewski has emphasized, should be kept clearly in mind when evaluating any reinfection experiments in syphilis, and for that reason we shall discuss first the information obtained by inoculation of the anterior chamber of the eye, and then that obtained by the more common intratesticular and subscrotal methods of inoculation, in untreated animals only.

*A First and second inoculations in the anterior chamber of the eye*  
Bertarelli was the first to carry out reinoculation experiments in syphilitic rabbits. Both first and second inoculations were made into the anterior chamber of the eye. In his first experiments (31) he used virus from human sources, hence heterologous, and in three rabbits which had previously had unilateral syphilitic keratitis he was unable to produce disease of the opposite (unaffected) cornea upon subsequent inoculation. In a second series of experiments (32) in which syphilitic virus was used that had been passed through rabbits and hence was presumably homologous, he inoculated corneas in which syphilitic keratitis had previously been present and in 1 of 4 animals keratitis developed. From these experiments he concluded that there is no absolute local immunity for corneal syphilis of rabbits. Truffi (33) inoculated one anterior chamber and both scrota of a rabbit and 147 days later, after the lesions had healed, reinoculated both anterior chambers and both scrota and obtained a negative result.

On the other hand, Purckhauer (34) obtained 3 successful reinoculations in rabbits that had had a syphilitic keratitis previously. He does not state whether or not he obtained any negative results and he concludes that corneal syphilis does not produce any immunity towards a second infection. From this conclusion he deduces that no generalisation of the syphilitic virus takes place in rabbits after ocular inoculation. Colombo (35) stated that a rabbit's eye, in which syphilitic keratitis has been produced and which has apparently healed spontaneously, can be reinoculated with success. Uhlenhuth and Weidanz (36) found that syphilitic keratitis of one eye does not, as a rule, protect the other cornea against infection, whether or not the diseased eye is enucleated prior to inoculation.

Unfortunately many of the details of the earlier experiments have been omitted from the authors' papers so that it is a well nigh hopeless task to attempt to analyse the conflicting results obtained by the various workers. About all that one can conclude with safety from this material is that some rabbits with healed corneal syphilis are resistant to a second ocular inoculation, while others are not, in other words, that the refractory state is not universal so far as the cornea is concerned.

*B First inoculation in the anterior chamber, second inoculation testicular or subscrotal* Uhlenhuth and Mulzer (37) inoculated the anterior chambers of the eyes of 4 rabbits with syphilitic virus and in all a bilateral keratitis developed. After the keratitis had healed spontaneously the animals were inoculated intratesticularly with virus from syphilitic rabbits and in 3 of the 4 orchitis subsequently developed. In a similar series of experiments Tomaszewski (38) obtained 5 successful reinoculations in 6 animals with healed syphilitic keratitis, the second inoculation being made with rabbit virus in the subscrotal tissue from 2 to 128 days after the keratitis had healed. In 17 rabbits with pre-existing syphilitic keratitis Adachi (39) obtained 8 successful reinoculations using the subscrotal method 41 to 120 days after the first infection.

From these experiments it would appear that syphilitic keratitis in the rabbit does not confer protection against a second infection introduced into the testis or scrotum.

*C First inoculation testicular or subscrotal, second inoculation in the anterior chamber* The results obtained when the first inoculation of syphilitic virus is made into the testis or the scrotum of the rabbit and the second into the anterior chamber of the eye have been conflicting. Uhlenhuth and Mulzer inoculated 11 rabbits intratesticularly, some unilaterally and some bilaterally, and subsequently inoculated them a second time by the intraocular route. The interval between first and second inoculations varied from 59 to 170 days. In some of the animals the orchitis was still active at the time the second inoculation was performed, in others it had healed. In only 1 of the 11 animals did the second inoculation result in a keratitis, in this instance after an incubation period of 25 days. Tomaszewski, on the other hand, obtained almost the opposite result. He inocu-

lated 21 rabbits subscrotally and in all of them syphilitic lesions developed. Second infections were then performed by the intraocular route from 39 to 105 days after the first inoculation. In 16 of the 21 animals, or 76 per cent, keratitis developed from 4 to 6 weeks after inoculation. He states that this incidence of positive reinoculations is almost identical with the incidence of infection obtained by him in normal rabbits inoculated in the same manner. More recently Frei (40) inoculated 25 rabbits subscrotally or intratesticularly, or by both methods and, after the lesions had healed, reinoculated by the intraocular route. The interval between first and second inoculations varied from 2 months to  $2\frac{1}{4}$  years. He obtained only 4 successful reinoculation results, or 16 per cent. In his experiments he employed homologous virus for the second inoculation. In a similar experiment Adachi (39) obtained 5 successful reinoculations in 18 rabbits.

It is difficult, if not impossible, to explain these conflicting results. The high percentage of negative results obtained by Frei, as contrasted with the numerous positive results of Tomaszewski, might be explained on the basis of longer interval between first and second inoculations but in that case the negative results obtained by Uhlenhuth and Mulzer are still to be explained. Careful scrutiny of the protocols of the experiments of the latter fails to disclose any way in which their results may be brought into harmony with those of Tomaszewski.

*D First and second inoculations testicular or scrotal.* In most of the studies dealing with reinfection in experimental syphilis of the rabbit, the testicular or subscrotal methods of inoculation have been employed. Truffi (41) was apparently among the first to conduct such experiments. In 1908 he inoculated a rabbit subscrotally with human virus and obtained a syphiloma which healed spontaneously. Five successive attempts at reinoculation of this animal by the same method yielded negative results. A sixth attempt, performed 514 days after the original inoculation, yielded a positive result. Altogether he reinoculated 6 rabbits and succeeded in producing a second infection in 4 instances, including the one mentioned. In these animals the second (successful) inoculation was made 12, 26, 76 and 514 days after the first. It is not clear from his article that all the negative results are recorded.

Ossola (42) reinoculated 4 syphilitic rabbits but failed to obtain a single positive result. In the case of 2 of the animals the interval between first and second inoculation was 56 and 106 days, respectively. In the case of the other 2 the time interval is not stated. Homologous virus was used for reinoculation in all 4 animals.

Uhlenhuth and Mulzer reinoculated 8 rabbits at intervals of from 53 to 178 days after the first inoculation and obtained what they regarded as successful reinoculations in 7. In 4 of these the lesion developed in the testis which had not previously been inoculated. No significant differences in the incubation period of first and second infections were noted. Reinoculations were apparently made with the same strain of treponemes. In the single instance in which a negative result was obtained the second inoculation was performed 178 days after the first.

Tomaszewski reinoculated 24 syphilitic rabbits at intervals of from 7 to 92 days with homologous virus, both first and second inoculations being made subscrotally, and obtained lesions in 18 animals. All those reinoculated before the sixty-seventh day of the disease gave positive results and none of those in which the second inoculation was performed after this time showed any signs of a second infection. The character of the lesions produced as a result of reinoculation varied, half of them were chancres and the other half papules. Tomaszewski interprets the occurrence of papules as an evidence of changed reaction capacity on the part of the scrotal skin.

Nichols reinoculated 5 syphilitic rabbits, the second inoculum being introduced into the opposite testis from that originally inoculated, and obtained what he regarded as second infections in 3 of the animals. The originally inoculated testis had been removed prior to reinoculation in 2 of these animals. In each instance the incubation period of the second infection was longer than that of the first.

Zinsser, Hopkins and McBurney (43) reinoculated 17 syphilitic rabbits, the homologous strain being used in 4 instances and a heterologous strain in 13. Altogether, lesions containing treponemes were produced in 3 instances and in a fourth chancres were produced but treponemes were not demonstrated. In 5 of the remaining 13 "small nodules" appeared following the second infection but the authors are in doubt as to the nature of these lesions since no treponemes were

demonstrated in them. The remaining 8 animals showed nothing at all following the second inoculation. The interval between the first and second inoculation was comparatively long, ranging from 38 to 458 days. In all but one instance this interval exceeded 100 days. The 3 undoubtedly successful reinfections obtained by these observers occurred in animals reinoculated with heterologous strains.

Fournier and Schwartz (44) concluded that rabbits in which syphilitic lesions have been allowed to heal spontaneously are refractory to a second infection with the same strain.

Brown and Pearce (45) showed that if untreated rabbits with bilateral syphilitic orchitis were inoculated by intracutaneous injection with the homologous strain of treponemes 24 days after the first inoculation, slight lesions were produced at the site of the second inoculation in a few instances. The lesions produced, however, were not comparable with those seen in the control animals, but they were regarded as syphilitic by these authors.

Kolle (46), on the basis of several hundred reinoculation experiments, has stated that if a second inoculation is carried out with homologous strains of treponemes (Truffi strain) within 60 days after the first inoculation, a typical chancre may be produced in 50 to 60 per cent of the cases. If the reinoculation is performed between the sixtieth and ninetieth day, occasionally a chancre is produced, whereas if it is carried out after the ninetieth day no lesion develops. Most of his reinoculations were by the intratesticular route but some were made upon the skin of the back. Frei obtained similar results. In 8 reinoculations performed before the twenty-eighth day of the disease with homologous strains, lesions were produced in every instance. In 7 performed 49 days after inoculation the result was negative in 4 instances and positive in the remaining 3, whereas in 52 rabbits in which the second inoculation was carried out from 63 days to 4 years after the first, all of the animals were refractory to a second infection.

Reiter (47) reinoculated 19 rabbits at intervals of from 133 to 602 days after the first inoculation and obtained 3 undoubted and 1 questionable reinfection. Ten of the reinoculations were made with homologous strains and 9 with heterologous strains. All of the successful reinoculations and the questionable one were obtained with heterologous virus. Chesney and Kemp (48, 49) reinoculated 8

rabbits with the homologous strain of treponemes from 270 to 336 days after the first inoculation and in no instance were they successful in obtaining any macroscopic lesions. Adachi (50) reinoculated 31 syphilitic rabbits 151 to 531 days after the infection and obtained 7 successful reinfections, all with heterologous strains, whereas all the reinoculations with homologous strains were negative. The same investigator produced chancres in a series of rabbits by uni-lateral scrotal inoculation. At varying intervals (3 to 43 days) after the appearance of the chancre the lesion was excised and used for inoculating the opposite testis. When the excision of the original chancre was performed earlier than 18 days after its appearance (thirty-first day of the disease) the other testis could be infected, whereas if excision were carried out 23 days or more after its appearance (forty-seventh day of the disease) the result was always negative.

From the foregoing it would appear that in rabbits a first inoculation made in the testis or scrotum confers upon the same or opposite testis or scrotum, protection against a second infection, provided a sufficiently long period of time is allowed to elapse between the first and second inoculations and provided homologous strains are used throughout. Under such conditions, as Kolle has pointed out, the percentage of successful second infections diminishes and almost reaches zero if the time interval between successive inoculations is increased.

The time at which this refractory state is fully established varies according to different observers, possibly due to variations in strains, but the main fact seems now to be well established. I have gathered together from the available literature all the reinoculation experiments in *untreated* rabbits with homologous strains of *T. pallidum*, where the intratesticular or subscrotal method has been employed for both first and second inoculations, and where the time interval between inoculations is expressly stated. These are summarised in table 1.

As will be seen from table 1, when the second inoculation is carried out between 20 and 60 days after the first, the percentage of successful reinoculations is 78.7, when the second inoculation is performed between the sixtieth and the ninetieth day of the disease the percentage falls to 11.4 and when it is carried out more than 90 days after the first the percentage is only 5. These figures bear out Kolle's results in untreated rabbits with remarkable accuracy.

The situation is somewhat different if heterologous strains are used for reinoculation. In that event a much higher percentage of reinfections is obtained, even if the second inoculation is performed late in the course of the disease, at a time when the rabbits would presumably be refractory to a second inoculation with homologous virus. This point has recently been emphasized by Kolle (51) although it was indicated previously by the work of Zinsser and his collaborators, of Brown and Pearce (52), and of Reiter. The results of the investigations of all

TABLE 1

*Reinoculations of untreated syphilitic rabbits with homologous strains*

AUTHOR	DAYS AFTER INOCULATION											
	20-60				61-90				91+			
	Number		Per cent		Number		Per cent		Number		Per cent	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Ossola	1	1	0	100					0	1	0	100
Uhlenhuth and Mulzer	2	0	100	0	2	0	100	0	3	1	75	25
Tomaszewski	11	0	100	0	1	6	14	86				
Nichols	2	2	50	50	1	0	100					
Zinsser et al									0	4	0	100
Frei	11	4	73	27	0	25	0	100	0	34	0	100
Reiter									0	10	0	100
Chesney and Kemp									0	8	0	100
Kolle			50-60				*				0	
Total	26	7	78.7	21.3	4	31	11.4	88.6	3	58	5	95

\* Kolle states that in reinoculations between the sixtieth and the ninetieth day typical chancres may be produced occasionally.

these workers, where the details are available, are summarized in table 2.

Study of table 2 shows that in more than a third of the untreated rabbits reinoculated with heterologous strains late in the course of the disease, a second infection may take place. Recent work by Adachi (50) and some as yet unpublished experiments of Chesney and Kemp (53) are in accord with this finding.

The experimental observations upon man, monkeys and rabbits, therefore, show that it is possible to produce second infections by inocu-



lating the host even after the appearance of the initial lesion, provided not too long a period of time is permitted to elapse before the second inoculation is carried out. As time goes on, however, the chances of producing a second infection diminish. The precise time limits during which it is possible to produce such a second infection vary somewhat with the different animal species and probably with the individual strains. The recent work with rabbits would indicate that in syphilis the refractory state toward a second infection which does develop with time is more marked toward the homologous strain of treponemes than toward a heterologous strain. It is possible that the refractory state appears at an earlier date in man than in monkeys or

TABLE 2  
*Reinoculations of untreated syphilitic rabbits with heterologous strains*

AUTHOR	REINOCULATIONS CARRIED OUT 90 DAYS OR MORE AFTER FIRST INOCULATION			
	Number		Per cent	
	Positive	Negative	Positive	Negative
Zinsser et al	3*	9	25	75
Reiter	4	5	44	56
Kolle	23	28	45	55
Chesney and Kemp	7	4	63.6	36.4
Total	37	46	44.5	55.5

\* One of these clinically positive but dark field negative

rabbits but this difference may be only apparent and may possibly be explained upon the basis of differences in method of inoculation, amount of virus in the inoculum, or again upon a less rapid generalization of the virus in the lower animals. Not much weight can be given to this last-mentioned possibility, however, since Pearce and Brown (54) have demonstrated that in rabbits migration of the treponemes from the site of inoculation takes place within a very short time (48 hours) after testicular or scrotal inoculation.

3 *Late period in Man.* Purposeful inoculation experiments upon syphilitic individuals who have had their infection for years, whether or not they showed tertiary lesions, have been comparatively few in number since the discovery of *Treponema pallidum*.

Finger and Landsteiner inoculated a series of 15 patients exhibiting tertiary lesions with material from human sources rich in treponemes. Inoculations were made by introducing the virus into subepidermal pouches. Lesions developed in 13 of the subjects at the site of inoculation. These did not resemble chancres but presented the clinical appearance of tertiary lesions (cutaneous tubercles, gummata and ulcerative syphilides), and were extremely poor in spirochetes. Inoculations with heat-killed virus were negative. Salmon (55) repeated these experiments on three subjects whose syphilis was of long duration (20 to 32 years), and who were actually exhibiting tertiary lesions at the time of inoculation. Altogether 8 inoculations were made upon the 3 patients. In one of the patients two small papules developed, the others remained free of any lesions. Nothing resembling a tertiary lesion was produced. Queyrat and Pınard (56), on the other hand, were apparently successful in one instance in producing a typical ulcerative syphilide by inoculating an individual having a tertiary lesion, with a small piece of a chancre placed in an intradermal pouch. The original infection occurred 7 years previously in this case and a period of 17 days elapsed between inoculation and the development of the lesion. No treponemes could be demonstrated in the lesion at any time. Likewise Vignolo-Lutati (57) succeeded in producing a gummatous lesion by inoculating a patient showing tertiary phenomena with a portion of a primary lesion, introducing the inoculum after the manner of Finger and Landsteiner. von Poor (58) inoculated 12 syphilitic individuals exhibiting outspoken tertiary phenomena with material taken from their own lesions but in no instance did anything develop at the site of inoculation. On the other hand Cappelli (29) was successful in producing an ulcerative lesion resembling a gumma in a patient whose syphilis was of 18 years duration. Krafft-Ebing (59) inoculated 9 paretics with material from early lesions but in no instance was he able to obtain any lesions at the site of inoculation. Siemens (60) inoculated 16 paretics and 3 tabetics a number of times (65 inoculations altogether) with syphilitic material, always with negative results, and Steiner (61) and also Sagel (62) were equally unsuccessful in a number of similar experiments. One successful inoculation was, however, reported by Jahnke (63) according to Steiner. According to the account given by the latter, the patient was a paretic whose blood

and spinal fluid had become negative after unusually intensive salvarsan treatment, inoculation of the skin of the arm with syphilitic material was followed by the appearance of two small lesions in which spirochetes could be demonstrated. It is clear that this one positive result must be regarded as an exception to the rule.

So far as the foregoing experiments go, they suggest that the late syphilitic is refractory to a second infection in the sense that new syphilitic virus introduced from without is incapable of producing a chancre followed by secondary manifestations. The most that they show is an altered capacity on the part of the tissues to react to the virus. We shall return to this interesting subject later.

*b Monkeys* Metschnikoff and Roux were unable to obtain successful reinoculations in apes in the later stages of the disease, and Finger and Landsteiner were likewise unsuccessful. In the hands of the latter the animals were still refractory 10 months after the first inoculation. As stated above, the incidence of positive reinoculations obtained by Neisser in monkeys was extremely low, actually only 3 in 114 experiments, or 2.6 per cent, when the second inoculation was performed after the 80th day of the disease. He obtained negative results when the interval between first and second inoculations was as long as 650 days. His results show clearly that in apes, at least, the resistant state, once acquired, persists for almost two years and for all we know may persist even longer.

*c Rabbits* As has been shown in a preceding section, where the question was discussed in greater detail, the state of resistance toward a second infection with the homologous strain of treponemes, which rabbits acquire as a result of their first infection, is well established in nearly all instances by the 90th day of the disease and has been shown to persist for at least 4 years (Frei). There are exceptions to this generalization, of course, but the principle seems to hold true in the main. This resistant state is definitely more effective against homologous strains of treponemes than against heterologous strains, although to be sure it is effective against even these latter in at least half of the cases.

In general it may be stated that the reinoculation experiments upon man, monkeys and rabbits carried out in the later stages of the disease tend to show that the untreated syphilitic individual ultimately

acquires a not inconsiderable resistance to a second infection. While in certain instances lesions have been produced by inoculating patients having tertiary syphilis with syphilitic virus, nevertheless these phenomena have the characteristics of late lesions rather than chancres, and are not followed by the familiar secondary manifestations.

### Summary

It may perhaps be well at this point briefly to summarize the foregoing data before passing on to more theoretical considerations as to the nature of immunity in syphilis.

The reinoculation experiments that have been carried out upon syphilitic human beings, monkeys and rabbits since the discovery of the *Treponema pallidum* all tend to show that the host gradually acquires a resistance, more or less complete, toward a second infection with the same microorganism if the disease is allowed to develop untreated. The time at which this resistant state is first manifest varies to some extent with the particular animal species under investigation but in general it may be said that it is already present to a high degree before the primary lesion has healed. It is certainly present during the period of secondary lesions and during the later years of the infection. There is no reason to believe that this acquired resistance may not persist for the balance of the life of the host in many instances, although it seems likely that it may be subject to fluctuations from time to time, and is not absolute.

There is some evidence to show that not all tissues of the body share equally in this resistance and there is good ground for the view that, in rabbits at any rate, it is more effective against homologous strains of treponemes than against heterologous strains. Above all, it is clear that the time factor is essential in the acquisition of this resistant state.

From what has just been said it must be admitted that the data derived from the modern experimental work in syphilis have not overthrown the older conception of the development of an acquired resistance, during the course of the disease, to a new infection. But, as we shall see presently, some of this later work has been instrumental in throwing light upon such interesting questions as the nature of this resistance, its distribution, and particularly its relation to persistence.

of infection This last question is of paramount importance from the standpoint of our theoretical conceptions of immunity in syphilis and in addition has an important practical bearing upon treatment and cure, as we shall see later

#### CO-EXISTENCE OF INFECTION AND IMMUNITY

As a result of his studies in syphilis in apes Neisser brought forward a new conception of immunity in this infection, a conception which has dominated this field up to the present time, although recently evidence has been forthcoming which perhaps casts some doubt upon the validity of Neisser's generalizations Briefly stated, this investigator came to the conclusion that the resistance which a syphilitic animal acquires during the course of its disease is dependent upon the persistence of active foci of syphilitic infection somewhere in its body, and disappears if these foci are eliminated If an animal previously infected with syphilis proved refractory to a second infection that fact in Neisser's opinion indicated that the animal still harbored the first infection, whereas if it were found to be susceptible to a second infection that finding meant that the first infection had been eliminated Accordingly Neisser took the ground that the reinoculability or non-reinoculability of an animal could be taken as evidence of the success or failure of treatment, that is to say cure or no cure To put it a little differently, if a treated animal could be successfully reinfected it should, according to Neisser, be regarded as having been cured, if it was still refractory to a second infection it had not been cured Neisser was firmly convinced that there is no such thing as true lasting immunity in syphilis, that is to say, an acquired immunity which persists in the absence of infection This conception is obviously of such fundamental importance from the standpoint of both theory and practice that it becomes necessary to subject the data upon which it is based to a critical analysis It must be clear to anyone that the matter is far from being one of academic interest only

Neisser's conception derives its support from two sets of observations made by him, first, the determination that untreated syphilitic apes which are refractory to a second inoculation can be shown to harbor the virus in their internal organs, second, that apes treated with various antisypilitic drugs and thought to have been cured, are at

once susceptible to a second inoculation, whereas other apes treated but thought not to have been cured remain refractory. These treated and reinoculated apes were regarded as having been cured or not, on the basis of the results of inoculation of normal animals with emulsions of the internal organs of *other* apes treated in a similar fashion. It is thus a question of comparison of results of reinoculation in one series of treated animals with the results of organ transfer in another series. It should be noted that in no instance did Neisser compare both methods in the same animal.

As regards the first point mentioned above, namely, the demonstration that untreated apes which are refractory to a second inoculation are still syphilitic, the evidence brought by Neisser is quite convincing. He removed internal organs from 29 syphilitic apes that had previously been shown to be resistant to a second inoculation and inoculated normal animals with emulsions of these organs. By this means he succeeded in demonstrating that the internal organs of 22 of these animals contained living syphilitic virus. In the case of the remaining 7 whose organs gave negative results it should be stated that many of the normal animals inoculated with this material died prematurely. It is clear from these experiments, therefore, that untreated apes that have acquired a resistance to a second syphilitic infection can be shown to harbor the virus in their internal organs in a large proportion of the cases (76 per cent in Neisser's experiments).

The second point that he makes, namely, that syphilitic apes treated and thought to have been cured are, in a high percentage of the cases, susceptible to a second inoculation with syphilitic virus, while apes treated but not cured are as a rule refractory, rests upon the results of a series of reinoculations upon 198 treated monkeys. These animals were treated with a variety of drugs and were then inoculated a second time. Second infections were produced in 107 instances (54 per cent), doubtful results were obtained in 9 (4.5 per cent), and negative results in 82 (41.5 per cent). The incidence of successful reinoculations in these *treated* animals, 54 per cent, is in striking contrast with that, approximately 6 per cent, obtained in a series of 145 *untreated* animals. Neisser assumed that those treated animals which proved to be susceptible to a second inoculation had been freed of their infection by treatment since organ transfer from other apes similarly treated

gave a large percentage of negative results. Likewise, treated animals which were thought not to have been cured, gave a high percentage of negative results on reinoculation. Again, these animals were assumed not to have been cured because of the large percentage of positive results obtained when emulsions of organs from other similarly treated animals were inoculated into normal animals. Actually, taking all his published protocols into consideration, it is found that Neisser reinoculated 198 treated apes and carried out organ transfers in 109 other treated animals. In general his protocols disclose a fairly close parallelism between positive reinoculation and negative organ transfer on the one hand, and negative reinoculation and positive organ transfer on the other. Taking all his therapeutic experiments into consideration, he obtained 54 per cent positive reinoculations and 71 per cent negative organ transfers. The animals in both of these groups he regarded as having been cured.

The crux of this argument, of course, lies in the justification for the assumption that the treated animals which later were shown to be susceptible to a second inoculation had been cured of their first infection by treatment and that those which later proved refractory to a second inoculation were not cured. Before granting that the results of organ transfer in one series of treated animals may be taken as indicative of what treatment had accomplished in another series of animals and then going on to draw deductions therefrom, one would want to know how many strictly comparable experiments there were. In other words, how many animals treated with *equivalent amounts of the same drug at the same time* were subjected to the reinoculation test on the one hand and how many to the organ transfer test on the other? Obviously if different dosages were used in the two groups where different criteria were employed, one would not be in a position to compare the results of treatment in these groups and hence one could not say with absolute certainty whether or not infection had been eliminated.

When the protocols of Neisser's experiments are examined from this standpoint one is disappointed to find that in many instances the reinoculation experiments and organ transfer experiments are not strictly comparable since different dosages were employed. Indeed, although he carried out the reinoculation test upon 198 animals treated after infection had been established, and the organ transfer test upon

87 other treated animals I have been able to find only 13 instances comprising observations upon a total of 90 animals, where the two tests were conducted upon series of animals treated with equivalent doses of the same drug. Moreover, it is not possible to determine from these otherwise strictly comparable experiments, whether the treatment was begun at corresponding periods in the course of the

TABLE 3  
*Comparison of reinoculations and "organprüfung" in treated apes (Neisser)*

TABLE	PAGE	REINOCULATION			ORGANPRÜFUNG		
		Negative (no cure)	Doubtful	Positive (cure)	Negative (cure)	Doubtful	Positive (no cure)
XXXIV	266	1		5	3		
			1	4	1		
		1	1	2	5	1	
		1			1		
				4	1		
				1	1		
				2	1		
XLI	273			4	1		
				3	2		
XLIV	275	1		2	1		
LVI		6		1	3		
		6	1				4
Text	261	17					1

NB In compiling this table only those experiments were selected which were strictly comparable as regards dosage

disease. To this point we shall return later for it is of capital importance as we shall see.

Those experiments of Neisser which are strictly comparable in so far as dosage is concerned, I have gathered together and placed in a single table (table 3) for the sake of comparison.

From a study of table 3 it is seen that, assuming that a successful reinoculation means cure and that a negative organ test means the same, there is complete agreement as to the results of treatment between the two methods of testing in 6 series, lack of complete



agreement in 5 and a question in the remaining 2 in which the results of reinoculation were equivocal. In justice to Neisser it should be stated that of those experiments in which the conditions were strictly comparable as regards dosage the total number of animals showing agreement between the two tests was 72, that showing failure of agreement 14, while the remaining 4 gave equivocal results

Another and perhaps even more important question in relation to the experiments of Neisser which must be taken into consideration before accepting the validity of his contention that a successful reinoculation means the absence of the first infection and a failure to reinoculate means its presence, is the question of the time at which treatment was instituted in his experiments. The recent work of Kolle (46), Frei (40), Chesney and Kemp (49) and Adachi (64) has brought out very clearly the necessity of paying attention to this factor. The experiments of all these investigators, performed upon rabbits, are in complete accord and have established the fact that the time in the course of the disease at which treatment is begun is of prime importance in determining the character of the response of the host to a second inoculation. Thus rabbits treated before the forty-fifth day of the disease can be successfully infected a second time in almost every instance. If treatment is begun between the forty-fifth day and the ninetieth day of the disease the response of the animals to the second inoculation is variable in that some are reinfected and some are not. If treatment is postponed until after the ninetieth day of the disease the rabbits are almost universally refractory to a second inoculation. In the light of this now well-established fact it becomes necessary to reexamine Neisser's data obtained from monkeys and to determine in each instance the time at which treatment was begun and the subsequent response of the animal to reinoculation. Indeed this necessity is suggested by Neisser's own work, for, although he does not stress the point, his own experiments show that he obtained a considerably higher percentage of successful reinoculations in *untreated* apes when the second infection was introduced before the eightieth day of the disease than when it was introduced at a later date. If one arranges his reinoculation experiments in *untreated* monkeys according to the time at which the second inoculations were carried out, it is seen that the incidence of

positive results was 16.6 per cent when an interval of not more than 80 days was permitted to elapse between first and second inoculations. When, however, the second inoculation was carried out after the eightieth day of the disease only 3 positive results were obtained in 114 animals, an incidence of 2.6 per cent (table 4).

It is apparent that if undoubted second infections to the extent of 16.6 per cent are obtained in untreated monkeys when the second introduction of the virus is made before the eightieth day of the disease, whereas only 2.6 per cent of the animals can be reinfected after this period, then one might expect a higher percentage of successful reinoculations in monkeys treated early in the course of the disease than in those treated later, since it has been shown that in rabbits the time at which treatment is begun influences profoundly the response to

TABLE 4  
*Reinoculations in untreated apes (Neisser)*

INTERVAL BETWEEN FIRST AND SECOND INOCULATION	TOTAL NUMBER	POSITIVE		NEGATIVE	
		Number	Per cent	Number	Per cent
<i>days</i>					
21-80	36	6	16.6	30	83.4
81-650	114	3	2.6	111	97.4

a second inoculation. It is, therefore, necessary to determine the time at which treatment was instituted in Neisser's experiments.

When one examines the protocols of his experiments in which treated monkeys were subjected to reinoculation, with reference to the time at which treatment was begun, one is disappointed to find that in many instances this information is lacking. I have been able to collect from his tables the records of only 18 animals in which the time elapsing between the first inoculation and the beginning of treatment was expressly stated or could be computed, although a total of 198 monkeys were treated and subsequently reinoculated in his therapeutic experiments. These I have arranged in tabular form (table 5).

Study of table 5 shows that, as a whole, the incidence of successful reinoculations in the animals treated by Neisser before the eightieth day of the disease (where this could be ascertained from the record) was 66 per cent, whereas in those treated after that date it amounted to

44 per cent While the number of observations cited is admittedly too small to warrant any broad generalizations, especially in view of

TABLE 5  
*Reinoculation results in treated apes (Neisser)*

TABLE	PAGE	ANIMAL NUM- BER	INTER- VAL BEFORE TREAT- MENT	REINOCULATION RESULT		DRUG
			<i>days</i>			
XXXVI	269	272	50	Negative		Phenylarsinic acid
		117	225	Positive		Phenylarsinic acid
		252	47	Positive		Phenylarsinic acid
XLIV	274	472	59	Positive		Arsenophenylglycin
		478	46	Positive		Arsenophenylglycin
		283	86	Negative		Arsenophenylglycin
			TREAT- MENT AFTER CHAN- CRE	FIRST REINOCULA- TION	SECOND REINOCULA- TION	
			<i>days</i>			
IL	299	597	129	Negative		Dioxydiamidoarsenobenzol
		606	106	Positive		Dioxydiamidoarsenobenzol
		608	113	Negative		Dioxydiamidoarsenobenzol
		619	2	Positive		Dioxydiamidoarsenobenzol
		622	5	Positive		Dioxydiamidoarsenobenzol
		624	8	Negative		Dioxydiamidoarsenobenzol
		567	223	Negative	Positive	Dioxydiamidoarsenobenzol
		568	223	Negative	Negative	Dioxydiamidoarsenobenzol
		604	171	Negative	Positive	Dioxydiamidoarsenobenzol
		616	4	Negative	Positive	Dioxydiamidoarsenobenzol
		577	168	Doubtful	Negative	Dioxydiamidoarsenobenzol
		620	14	Doubtful	Negative	Dioxydiamidoarsenobenzol

*Recapitulation*

INTERVAL BETWEEN FIRST INOCULATION AND TREATMENT	TOTAL NUMBER	POSITIVE		NEGATIVE	
		Number	Per cent	Number	Per cent
<i>days</i>					
Less than 80	9	6	66 6	3	33 3
More than 80	9	4	44 4	5	55 6

the total number of animals studied, nevertheless their tendency is to indicate that in monkeys the earlier treatment is begun the more apt

is the animal to yield a positive result on reinoculation. Therefore it would seem highly desirable to take into account this factor of the amount of time elapsing between the original inoculation and the institution of treatment, before admitting that Neisser's results indicate that the reinoculation test is a valid criterion of cure. It is greatly to be regretted that the published protocols of Neisser fail to give the information which is necessary to clear up this question in so far as monkeys are concerned, and thus permit one to decide whether the criticism which is implied in the foregoing analysis is justified.

There is still another question which the recent work on reinfection in syphilitic rabbits makes it necessary to raise in regard to Neisser's reinfection experiments in monkeys, and that is the question of whether Neisser used homologous or heterologous strains for reinoculation. Kolle has demonstrated conclusively that rabbits infected with one strain and not treated may, in a large proportion of the cases, be successfully infected with another strain, even if the second infection is introduced comparatively late in the course of the disease. In some as yet unpublished experiments Chesney and Kemp have obtained similar results with heterologous strains in treated as well as untreated rabbits. It is by no means clear from Neisser's protocols whether he used homologous or heterologous strains in his reinoculation experiments in treated monkeys.

In the absence of data upon the points which we have raised, namely the time at which the animals were treated and the character of the strain used for reinoculation, it may perhaps seem wiser to some to consider that, in so far as apes are concerned, the contention of Neisser to the effect that in syphilis the acquired refractory state is dependent upon residual infection and disappears coincidentally with the elimination of that infection, has not been finally proved.

It would indeed seem rather strange, in view of what is known concerning the principles of immunity in general, if the resistance acquired as a result of syphilitic infection were sufficiently great to protect the animal against really large doses of a second infection, and yet vanish at once after the first infection had been eliminated. One would scarcely expect that such a profound change in the reacting capacity of the body toward new virus as is exhibited by the syphilitic animal, would disappear rapidly. Yet Neisser says that treated monkeys be-

come reinoculable immediately ("sofort") Certainly one would not be justified in predicting such a result in syphilis on the basis of immune principles that obtain in most other infections

If one takes the ground that this question of the dependence of immunity in syphilis upon the persistence of foci of infection has not been definitely settled by the earlier work upon monkeys, one may inquire as to what data bearing upon this point are available from studies of the infection in rabbits, and what data are afforded by the clinic with its opportunities for the observation of reinfections in man

With regard to the first of these two questions, recent work, as stated previously, has clearly demonstrated that the time at which treatment is begun in the course of experimental syphilis of the rabbit has an exceedingly important bearing upon the response of the animal to a second inoculation Kolle was the first to emphasize this point, although Brown and Pearce (65) had previously shown that treatment 18 days after inoculation with subcurative doses of arsphenamine or neoarsphenamine renders the rabbit susceptible to a second infection introduced 6 days later Kolle demonstrated clearly that if syphilitic rabbits were treated with antisyphilitic drugs before the forty-fifth day of the disease they were almost uniformly susceptible to a second inoculation, whereas if the treatment were begun after the ninetieth day they were almost uniformly refractory to a second inoculation If the treatment were begun at some time between the forty-fifth and the ninetieth day, some of the animals were refractory and some were not The same results were obtained whether the treatment was short or prolonged

Adhering to Neisser's views regarding immunity in syphilis and the validity of the reinoculation test as a criterion of cure, Kolle interpreted his own results as indicating that abortive cure of syphilis in the rabbit is possible with certainty only when treatment is begun comparatively early in the course of the disease, that is to say before the forty-fifth day, and impossible if it be postponed until after the ninetieth day. Frei obtained analogous results but was careful not to draw the conclusion that failure to reinoculate an animal meant failure to cure. He emphasized the importance of carrying out control observations with organs of treated animals but was unable to do so Chesney and Kemp (48, 49) went a step further They confirmed the obser-

vations of Kolle and of Frei to the effect that early treatment with arsphenamine leaves the animal susceptible to a second inoculation, whereas the late-treated animals remain refractory, but they showed in addition that the lymph nodes of these *same* animals were (through treatment) rendered incapable of transmitting the disease to normal rabbits, irrespective of the time at which treatment was begun. In other words, even if treatment were postponed until six months after inoculation, it was nevertheless apparently effective in sterilizing the lymph nodes and yet the *same animals* were subsequently shown to be refractory to a second inoculation. These observations suggested the possibility that in rabbits, at least, there may be such a thing as an acquired immunity resulting from syphilitic infection which persists in the absence of demonstrable infection, a view to which Adachi (64) subscribes.

Here again, the question of whether or not the treatment, when given late in the course of the disease, was effective in eliminating entirely the infection from the rabbit's body, constitutes the crux of the matter. Is lymph node sterility following treatment a certain index of cure? This is admittedly an exceedingly difficult question upon which to pronounce a definite opinion.<sup>4</sup> In a further series of experiments in which emulsions of lymph nodes and internal organs from untreated and late-treated rabbits were inoculated into normal animals, Chesney and Kemp (66) obtained evidence which suggested that the same treatment was effective in rendering those organs tested (heart, liver, spleen, bone-marrow, and brain), as well as the lymph nodes, non-infectious in a large majority of the animals. In all their experiments care was taken to maintain strictly comparable relations as regards dosage of drug and time of administration. The results of their experiments as to the efficacy of arsphenamine and its modifications in sterilizing lymph nodes were in strict accord with those obtained previously by Nichols and Walker (67) and also by Voegtlin, Armstrong and Dyer (68).

Chesney and Kemp (69) have obtained additional evidence which casts doubt upon the validity of the remoculation method as a criterion

<sup>4</sup> A recent communication by Worms (160) shows how careful one must be in drawing conclusions as to cure, from the transfer of lymph nodes from treated animals to normal animals.

ion of cure They found that while rabbits, which were originally inoculated in the testis and treated late in the course of the disease, were almost uniformly refractory to a second intratesticular inoculation, other syphilitic rabbits similarly treated and reinoculated by a different method (deposition of virus upon a granulating wound on the back) were in 50 per cent of the cases susceptible to a second infection. In other words, the mode of reinoculation in treated animals as well as the time at which treatment was begun was found to play an important rôle in determining the response of the animal to a second inoculation. If markedly divergent results from reinoculation are obtained in otherwise comparable groups, depending upon the particular method selected for reinoculation, it is at once apparent that no conclusion can be drawn, as to the presence or absence of the first infection, from the response of an animal to reinoculation

It would appear from the recent work with rabbits therefore, that the validity of the reinoculation test as a criterion of cure of syphilis in the rabbit has definitely been brought into question, a statement that is supported by a recent communication from Voegtlin's laboratory (70) It necessarily follows that the contention of Neisser as to the inter-dependence of syphilitic immunity and active syphilitic infection is likewise brought into question It may not be amiss to point out that as long ago as 1865 Rollet (11) took the stand that immunity to syphilis does not necessarily imply the existence of syphilitic infection, and many years later Finger (71) expressed the same idea. Indeed Neisser's contention has not been without its critics (72, 73) even in recent years, although in general his idea has been almost universally accepted by syphilologists and immunologists as well

As suggested previously it may be of interest to ascertain what clinical observation has to contribute to the question That second attacks of syphilis do occur has long been known, but the number of such cases has been extremely small This relative infrequency of second attacks of syphilis was thought by Neisser to be due, not to a true immunity surviving after the infection had been eliminated, but to two other factors first, that the number of uncured cases of syphilis is greater than was formerly realized, a contention which the data supplied by the Wassermann reaction would seem to uphold, secondly, that there is less exposure to infection with advancing years

of life by reason of changing social relationships, especially that of marriage. Whether these two factors together would be sufficient to account for the great infrequency of second attacks of syphilis is, and probably always will be, a matter of speculation. But it is also possible that this infrequency may in part be explained upon the basis of an acquired immunity persisting throughout life, even after total eradication of the infection by suitable treatment. Clinical experience in respect of reinfections is certainly not in conflict with this conception.

There seems to be general agreement that the number of undoubted instances of reinfection is greater now than before the introduction of salvarsan. This fact has been urged by some as an index of the greater efficacy of this drug over older forms of treatment, and has also been utilized by those who adhere to Neisser's view of the inter-relationship between persistent infection and immunity. Briefly their argument is as follows. More cases of reinfection are seen now than formerly because more patients are cured and hence become susceptible again to syphilis. It must be obvious that this argument does not dispose of the conception of acquired immunity to syphilis persisting in the absence of infection, since it is conceivable that in many cases treatment with salvarsan might be, and doubtless is, postponed until a considerable time interval has elapsed after infection, during which interval a considerable degree of resistance may have been acquired by the host, and yet the latter might nevertheless have been cured. In other words, in man, as in the rabbit, the time at which the first infection comes under treatment may be the all-important factor in determining the response to a second infection, and *ipso facto* the number of cases of reinfection which will be encountered in the clinic. In view of this possibility it becomes important to ascertain the time at which treatment was first begun in the cases of reinfection that are recorded in the literature. If one could assemble a large number of cases of undoubted reinfection in which the patient had not received treatment for his first infection until a comparatively late date in the course of his disease, say the latent period following the healing of the secondary lesions or the tertiary period, one would have to admit that the case for the existence of syphilitic immunity in man in the absence of syphilitic infection would be greatly weakened if



not altogether demolished. Actually, however, no such array of cases has as yet been assembled

By far the overwhelming majority of cases of undoubted reinfection that have been reported thus far have occurred in patients in whom treatment was begun early in the course of the disease. The undoubted instances in which a patient was treated for the first time late in the course of his infection and subsequently contracted syphilis a second time are exceedingly few in number, although by now the literature contains many examples of undoubted reinfections. Benario (74) in 1914 was able to gather together from the literature of 1910-1914, 96 cases of undoubted syphilitic reinfection. These cases were rigidly selected. All of these patients had been treated with salvarsan alone or in combination with mercury. Patients treated with mercury alone were not included in his report. In all but one of these the treatment for the first infection was begun during the early stages of the disease. In the one exception the first infection dated back 23 years prior to treatment with salvarsan. At the time this particular patient received his first dose of salvarsan there were no physical signs of syphilis but the Wassermann reaction was positive. One may object to this evidence upon the ground that at the time Benario collected his cases there had not yet been opportunity for a sufficiently large number of patients with late syphilis to have been treated with salvarsan and become reinfected, and that the number of early cases treated up to that time was far in excess of the number of late cases treated. There are, of course, no data on this point, but a survey of the cases of reinfection reported in the literature since 1914 indicates essentially the same situation disclosed by Benario. Dr H Wasserman has, at my suggestion, undertaken from this standpoint a survey of the cases of reinfection reported in the literature since the appearance of Benario's communication and also the reinfections encountered in the syphilis clinic of the Johns Hopkins Hospital. While that survey is not as yet complete, it has progressed sufficiently far to show that practically all the cases of undoubted reinfection have occurred in individuals who received treatment for their first infection early in the course of their disease.

Clinical experience in respect of syphilitic reinfection in man, therefore, does not controvert the idea that in this infection an immunity

may develop in time which will persist after the infection has been abolished. It is obvious, however, that the same experience may be interpreted as indicating that cure of syphilis in human beings is possible only when treatment is begun early in the course of the disease and not at a later date. At present it is not possible to say, from the data available from human sources, which interpretation is the correct one.

The question of the development in human beings of a true immunity to syphilis has recently been discussed by Kolle (51) from a new angle. Upon what might perhaps be called epidemiological grounds he seems to have come to the conclusion that human beings do acquire a true immunity during the course of an attack of syphilis. His conclusion is based upon the following argument. According to him, sterilization of the syphilitic individual by means of antisypilitic agents, especially salvarsan in combination with mercury, is possible in a large proportion of the cases when treatment is begun early. If immunity of human beings to syphilis is dependent only upon latent infection, then many cases of reinfection ought to be encountered since modern treatment of the early syphilitic often leads to complete cure, according to Kolle. Granted that in Germany, during the course of a year, only 10 to 20 per cent of persons with early syphilis receive abortive treatment and hence are cured, then in the course of time one should see in that country many thousands of cases of reinfection occurring in cured individuals who cannot, because of cure, be considered as having a latent infection and an immunity dependent thereon. Actually, however, one does not see any great number of such cases of reinfection. They are in reality very scarce. Kolle, therefore, concludes that this scarcity is dependent upon an acquired immunity which develops in the syphilitic during the course of his infection and persists after a mode of treatment which he thinks effectually eliminates the disease.

It is obvious that the validity of Kolle's conclusion rests upon the truth of two premises, one of which is expressed, the other implied, first, that early treatment of syphilitic human beings with the modern means of attack does result in biologic cure in a large proportion of cases, second, that those individuals who have been infected and are promptly and adequately treated continue to be exposed to infection

after treatment has ceased, and indeed that exposure occurs about as frequently as before infection. Most syphilologists will probably assent to the first of these two propositions, namely that syphilis in the human being can be cured with early and systematic modern treatment. As regards the truth of the second proposition, that individuals who have once contracted syphilis and been treated for it continue to be exposed to the same infection to something like the extent obtaining prior to their having contracted the disease, that question must necessarily be a matter of conjecture since we are not likely ever to have any accurate data upon it. Nevertheless, Kolle's argument implies that such continued exposure does actually take place in Germany, and there is every reason to believe that the same state of affairs obtains for that portion of the American population in which syphilis is most prevalent. Certainly Kolle's argument is unique, suggestive and rather convincing.

Kolle concludes from the same train of reasoning that the immunity which the human being acquires as a result of his infection is effective against heterologous strains as well as the homologous strain, and he regards it as of a higher or different order than that which rabbits acquire and which for the most part is effective against homologous strains only. Before placing relative values upon the resistance which develops in man and that which develops in the lower animals in the course of syphilitic infection, it may be well to recall that doses of virus are used in performing reinoculation experiments upon the latter which may exceed any that human beings are apt to encounter, furthermore, the mode of inoculation is quite different, and in the experimental infection certainly favors the invading microorganism rather than the host. In short, apparent differences in degree of acquired immunity to syphilis as seen in man on the one hand, and in the monkey and the rabbit on the other, may possibly be resolved upon the basis of the size of the inoculum of the second infection, or the mode of its introduction. Further studies on the quantitative relationships of this problem are highly desirable.

It may be of interest at this point to call attention, in passing, to a recent communication by Prigge (75) from Kolle's laboratory, in which support is advanced for the view that the immunity which mice, that have recovered from relapsing fever, exhibit toward a second in-

fection, is a true immunity, and is not dependent upon residual foci of infection in the brains of these animals, a view that had been proposed by Buschke and Kroo (76)

*Summary* The conception that acquired immunity in syphilis is dependent upon foci of syphilitic infection somewhere in the body was first advanced by Neisser upon the basis of experiments on monkeys. Analysis of his experiments in the light of recent contributions to this subject has raised the question as to whether or not his conception is justified. More recent work based upon experiments on rabbits would seem at present to controvert this view and to indicate that in syphilitic infection there may develop an immunity which is not dependent upon the persistence of foci of infection. Clinical experience in respect of reinfections in man is entirely in harmony with such a conception. The whole question is in intimate relation with that of the curability of syphilis, a problem which is most difficult of solution when the term cure is used in the biological sense. Perhaps it may be well for the present to take the ground that this particular phase of the problem of immunity in syphilis is still an open question, but it must be admitted that evidence is now being accumulated which would indicate that during the course of syphilitic infection the host acquires a resistance against a second infection with the same species of microorganism, a resistance which may persist after the first infection has been eliminated by treatment, or at any rate reduced to the level where it cannot be detected. If the truth of this proposition becomes firmly established, it will follow that reinoculation tests in animals or the occurrence of reinfections in man have no bearing upon the question of persistence or absence of infection, that is to say of cure or failure of cure, but are useful only as indicators of specific resistance. Logically speaking, in any case all that one can justifiably conclude from failure to reinfect an animal with syphilis is, that the animal is resistant to that infection.

### *Criteria of reinfection*

In almost all of the experiments dealing with syphilitic reinfection in animals the criterion of a successful reinoculation has been the production of a syphiloma at the site of reinoculation accompanied by the demonstration of treponemes in the lesion. This is, of course,

the safest criterion In dealing with reinfections in man it has generally been considered necessary to go a step further and demand that the lesion produced at the portal of entry be followed by evidences of systemic infection No one can object to the utilization of the most rigid criteria when dealing with possible reinfections in man However, since the tendency of syphilis to pursue a variable course, even during its early phases, is well known, and since syphilitic infections are known to occur in man without any lesion at the portal of entry and such infections can be produced in certain of the lower animals, it is theoretically possible that reinfections might pursue a similar course, nay more, there might be an even greater tendency for reinfections to manifest themselves in such a manner Neisser himself admitted this possibility but stated that he had never observed an example of it Brown and Pearce (77) called attention to this matter several years ago and pointed out that the development of a chancre in a reinoculated animal "is of more value as an index of the ability to produce a manifestation of disease than of infection, and that infection can not be excluded upon this basis" They went on to say "It would appear, therefore, that before the results of super-inoculation experiments can be made clear, the subject must be approached from a broader point of view and that evidence must be adduced which will enable one to see beyond the reaction at the site of inoculation "

This problem lends itself to study better in treated than in untreated animals Chesney and Kemp (69) have assembled evidence which indicates that it is possible to reinfect a treated rabbit without producing any lesion whatsoever at the site of reinoculation Nevertheless, in the hands of these investigators such animals give evidence of systemic invasion by the treponemes as evidenced by lymph node transfer, and in a large proportion of the cases a positive Wassermann reaction appears in the blood It would seem from their work that at least two factors may be involved in bringing about such an altered response to a second inoculation, these are (1) the time at which treatment is begun, and (2) the manner in which the second inoculation is made It is not inconceivable that the richness of the inoculum in treponemes or the virulence of the organisms may also constitute factors in producing such a response but as yet there are no data upon these points Voegtlin and Dyer (70) have also obtained results in

syphilitic rabbits treated with arsphenamine or sulpharsphenamine and then reinoculated with the same strain of treponemes, which lend support to the view that reinfections may occur without local lesions. More recently Kolle (78) has raised the same question and has indicated that he possesses evidence, which as yet has not been published, to the effect that second infections can be produced without the appearance of any local lesion at the portal of entry.

On the basis of their observations Chesney and Kemp have suggested that some of the relapsing Wassermann reactions occurring in patients with early syphilis who have been well treated may represent not a relapse of their first infection, as is generally held, but a true reinfection in which no lesion occurs at the portal of entry but in which systemic distribution of the virus takes place and is accompanied by the reappearance of a positive Wassermann reaction. In other words, a second infection may have taken place in such individuals and have undergone an unusual course by reason of the fact that it was introduced into a patient still under the influence of an immunologic change brought about by the first infection. Such individuals, if they exist, might be regarded as partially refractory to a second infection. It must be admitted that at present in clinical practice we have no means of differentiating such patients from those in whom the subsequent re-appearance of a positive Wassermann reaction represents a true serological relapse but the future may supply us with the means. For the present, however, in dealing with human beings, it would seem best to confine ourselves to the older and safer criteria of reinfection and demand a characteristic primary lesion followed by the evolution of secondary manifestations. In the experimental animal, however, it is probably not necessary to demand visible macroscopic lesions at the site of reinoculation before concluding that the animal has been reinfected, for in the case of the latter there are available methods, not applicable to the patient, of determining that infection and dissemination of treponemes has occurred.

#### ACTIVE IMMUNITY ARTIFICIALLY ACQUIRED

Active immunization as a therapeutic measure in syphilis was attempted in France as early as the first half of the last century. Doubtless the success attending small-pox vaccination was largely

responsible for the attempt Auzias-Turenne (79) conceived the idea of performing successive auto-inoculations upon patients with chancres in order to prevent the occurrence of secondary lesions and to this procedure he gave the name of "syphilization" He thought he was successful in preventing constitutional syphilis in this way but it is clear that he must have been working with material in which pyogenic organisms were present and his results failed of confirmation by others Nevertheless, a rather widespread and bitter controversy arose in France over the merits of the method but it quickly fell into disrepute and is of historical interest only at the present time

The recognition of the causal agent of syphilis and the transmission of the infection to animals gave further impetus to the attempts to immunize against the infection but, although a considerable number of experiments have been performed, the results have thus far been disappointing In presenting this phase of the subject we shall find it profitable to approach it from the standpoint of the nature of the material used for immunization

*Filtrates and extracts* De Luca and Casagrandi (80) injected 6 human volunteers intramuscularly with filtrates of primary lesions Two of these individuals later contracted syphilis after exposure to infected persons, although the remaining 4, in spite of opportunity for infection, remained free of symptoms while under observation Unfortunately, the period of observation was relatively short (2 months) The extracts had no therapeutic effect on patients with secondary lesions Metschnikoff and Roux (81) injected a chimpanzee with the filtrate from several human syphilitic lesions diluted with the aqueous humor of a sheep but were unable to obtain any evidence of immunity in the animal since a subsequent inoculation with non-filtered virus produced disease Neisser extracted chancres, condylomata and the organs of syphilitic fetuses with normal salt solution containing 0.5 per cent phenol and attempted to immunize apes with such extracts but obtained no evidence of immunity whatsoever Even when the test virus was inoculated at the same spot where the immunizing extract had been injected, a lesion made its appearance, indicating the powerlessness of such extracts to confer even a local immunity Furthermore, injections of these extracts carried out during the incubation period failed to prevent the development of syphilitic lesions

Truffi (82) injected rabbits with extracts prepared from dried pulverized livers of syphilitic fetuses in an attempt to immunize these animals against syphilitic infection but was unsuccessful. It is possible to say, therefore, that various manipulations of syphilitic tissue containing treponemes have not thus far yielded substances with any appreciable antigenic power so far as preventing or modifying the course of syphilis is concerned.

*Killed virus* Metschnikoff and Roux (81) inoculated a chimpanzee with virus from human sources killed by heating to 51°C for an hour. A subsequent inoculation of the same animal with active virus resulted in the development of a characteristic syphilitic lesion, indicating that heat-killed virus has no immunizing power in this species of animal. Finger and Landsteiner attempted to immunize 3 monkeys with subcutaneous injections of heat-killed virus but were unsuccessful in each instance. Equally fruitless were the attempts of Uhlenhuth and Mulzer to protect rabbits against syphilitic infection by the subcutaneous and intravenous injection of syphilitic virus killed by phenol or antiformin. They found also that a vaccine prepared from the testis of a syphilitic rabbit by drying the finely divided tissue on a glass plate and then suspending it in salt solution was equally ineffective in protecting rabbits against a subsequent inoculation with living syphilitic virus. Such vaccines when administered to rabbits already inoculated with syphilitic virus failed to exert any effect upon the course of the disease.

*Living virus* Of interest are the attempts of Spitzer to prevent the development of generalized lesions of syphilis in man by active immunization with living virus from patients presenting primary lesions. This procedure was undertaken at the suggestion of Kraus who thought that he saw a resemblance between rabies and syphilis in that in both diseases, as he supposed, a comparatively long interval elapsed between infection and generalization of the virus. Accordingly Kraus concluded that immunization of human beings with syphilis as soon as the diagnosis could be made and before the outbreak of secondary lesions, utilizing living virus, might prevent the occurrence of constitutional symptoms just as immunization of human beings with rabies during the incubation period often prevents the development of symptoms of that disease. The hypothesis was put to the test by



Spitzer (83) who treated a series of syphilitic patients with injections of emulsions of human chancres, using 2 cc of 1:200 dilution and increasing the concentration to 1:40. From 11 to 20 injections were given and in a series of 20 patients Spitzer claimed that secondary lesions failed to appear in 7 instances (35 per cent), although the patients were under supervision for a period of many months, the maximum period of observation being 2 years. One of the patients was thought later to have contracted a second attack of syphilis, a significant observation if true. The method was tried by Brandweiner (84) and also by Kreibich (85), both of whom reported unfavorable results. As Neisser has pointed out, in criticising this form of treatment upon theoretical grounds, generalization of the infection has already taken place by the time the chancre has made its appearance and the treponemes are being distributed all over the body by the circulation. Under these circumstances it seems unlikely that the subcutaneous injection of additional syphilitic virus in comparatively small amounts would hasten the development of the immune reaction of the host or accentuate it. Similar treatment of apes by Neisser, as we shall see presently, proved to be wholly ineffective, and this fact alone would make one extremely skeptical of the value of the procedure in man. Still, as Zinsser says, it is the only ray of light in what is otherwise a rather dark situation, but perhaps it is not a very bright ray.

Metschnikoff and Roux (86) sought to attenuate the virus of syphilis by passage through lower apes with the intention of utilizing such virus for immunization purposes. Indeed they came to the conclusion that they had been able to secure attenuation to such an extent that the virus was capable of producing in rhesus monkeys a comparatively insignificant lesion at the portal of entry which was not followed by any evidence of generalization of the infection. Nevertheless, the monkeys were refractory to a second inoculation. They thought, by an experiment upon a human volunteer, that they had secured attenuation of the virus for the human being as well. Neisser criticized their experiments rather vigorously in the light of his own work and suggested that Metschnikoff and Roux had not appreciated the fact that in the monkey, infection and generalization of the disease could occur although the lesion at the site of inoculation might be small or even non-existent. Neisser himself was unable to obtain the

slightest evidence of attenuation of syphilitic virus, either by passing it through monkeys or by treating it with chemical agents which themselves were not treponemicidal <sup>5</sup>

Finger and Landsteiner inoculated 2 monkeys with living virus, introducing the material deep into the muscles and then cauterizing the needle tract. No syphilitic lesion developed along the tract in either animal. Subsequent inoculation with living virus by scarification of the skin gave a positive result in one of the animals and a negative result in the other. Three monkeys inoculated intraperitoneally by them before or at the time of a cutaneous inoculation proved refractory to the latter. Neisser in a large series of experiments on monkeys found that the subcutaneous or intravenous injection of living virus at the time of the first (cutaneous) inoculation failed absolutely to prevent the development of a primary lesion at the site of the latter, furthermore, the same methods employed after the primary lesion had developed failed to prevent dissemination of the virus throughout the body.

In the hands of Uhlenhuth and Mulzer intravenous inoculation of living syphilitic virus failed to protect rabbits against intratesticular inoculations carried out 18 and 35 days later. Subcutaneous injection of living virus also failed to protect against intratesticular inoculation 50 days later.

*Cultures* It was natural that the successful cultivation of *Treponema pallidum* from human lesions should be followed by attempts to immunize animals with these cultures and to approach the study of immunity in syphilis by their aid. However, in spite of the large amount of time and effort expended, the results have in the main been disappointing. Nakano (89) gave 3 patients with early syphilis subcutaneous injections of killed cultures of treponemes but was unable to observe any influence upon the course of the disease in these patients. In his hands rabbits injected intravenously with cultures of treponemes exhibited agglutinins in their serum, the maximum titer reached being 1:60, nevertheless some of the immunized animals

<sup>5</sup> The occurrence of syphilis in laboratory workers, brought about by accidental infection with virus that had been carried through many generations of animals does not support the view that attenuation of syphilitic virus for man is accomplished by passage through other animal species (87, 88)

proved later to be susceptible to intratesticular inoculation with virus from rabbit testes in spite of the presence of agglutinins for treponemes in their blood Zinsser, Hopkins and McBurney (90) succeeding in producing agglutinating sera of high titer (1 2000 to 1·4000) by intravenous immunization of rabbits with cultures of treponemes but, like Nakano, found that their animals were still susceptible to intratesticular inoculation with virulent syphilitic virus They found also that intratesticular inoculation of rabbits with living cultures of treponemes failed to protect the animals against subsequent (intratesticular) inoculation of virulent treponemes obtained from syphilitic rabbit lesions.

Grouven (91) treated 2 syphilitic rabbits with Sowade's mixed cultures of treponemes and thought he observed a favorable effect upon the syphilitic lesions of both animals as evidenced by rapid healing He likened the effect to the focal reaction observed at times after the injection of tuberculin In spite of this apparently favorable result one of the animals subsequently exhibited recurrent lesions and it seems doubtful if the treatment had any real effect upon the course of the infection. In the hands of Schereschewsky (92) the injection of killed cultures of treponemes treated with antiformin appeared to protect 2 rhesus monkeys against a subsequent inoculation with virulent syphilitic virus from human sources but the injection of a culture containing living treponemes failed to protect a third monkey against the same virus It should be noted that in these experiments the animals were observed for only six weeks after inoculation, a rather short time in experiments of this sort Noguchi (93) thought that repeated intratesticular injections of rabbits with cultures of treponemes or killed virus from lesions reduced their susceptibility to syphilitic infection "to some extent," but since at least half of the animals thus treated were successfully inoculated later with virulent syphilitic virus the degree of resistance established by this method of immunization cannot be regarded as of a high order.

Sagel (62) has recently reported upon a series of 10 paretics treated with subcutaneous and intracutaneous injections of living treponemes, (cultures or rabbit virus), also by scarification with the virus His idea was that perhaps by bringing living syphilitic virus in contact with the skin a greater immune response to the infection might be

elicited and a favorable effect exerted upon the course of the disease process in the brain. The patients selected for this method of treatment had not shown any improvement following the production of artificial relapsing fever and they were regarded as having a hopeless prognosis. Of the 10 patients, 7 showed clinical and serological improvement, 1 showed serological improvement only and the remaining 2 showed no improvement. It is obvious that these patients have not been followed for a sufficiently long period of time to determine the final outcome and no judgment as to the method can be formed as yet. In none of the patients were syphilitic lesions produced at the site of inoculation and the method would certainly appear to be harmless.

*Summary* From the foregoing it is clear that there is general agreement among all the workers who have attempted to produce active immunity to syphilis in man, monkeys or rabbits. The almost universal experience has been that of failure, no matter what kind of material has been employed as antigen. Extracts of tissue containing treponemes, killed virus, living virus, cultures of treponemes, all as a rule have proved incapable of rendering the animal immune to a subsequent inoculation with virulent organisms. The experiments of Schereschewsky and of Noguchi are too few in number to invalidate this statement. In the few instances in which apparently successful results have been reported after the use of living "attenuated" virus it is by no means certain that the investigators had excluded the possibility that a general infection had been established and that the apparent immunity which they observed was the result of actual infection which had been overlooked. Nor has it proved possible to alter the course of an existing syphilitic infection by immunization with any product derived from cultures of treponemes or from syphilitic tissue. While it is true that Spitzer claimed to have modified the course of syphilis in human beings by active immunization during the early period of the disease with living virus from human sources, and favorable results have been reported by one observer who treated a small series of paretics with living syphilitic virus, the observations of these workers have not been confirmed and the method has not as yet found any recognized position in the treatment of syphilis.

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## PASSIVE IMMUNIZATION

If the manifold attempts actively to immunize man and animals against syphilis by the introduction of virus or virus-products have thus far been destitute of any significant results, it might be expected that the serum of such animals would fail to exert any protective or curative action in the natural or experimental disease. Unhappily the facts bear out that expectation. Attempts to bring about passive immunization against syphilis were made long before the causal agent of the disease had been discovered or the infection had been transmitted to lower animals. A curative serum was sought in human beings that had had the disease as well as in animals inoculated with syphilitic tissue. The earlier work has been summarized by Neisser (94) and it is unnecessary to discuss it here in any detail. Some of the procedures attempted in the past appear now as very bizarre. In spite of the extravagant claims of some workers the ultimate results of all this work were valueless. With the successful transmission of syphilis to lower animals interest was renewed in the subject since the production of an experimental infection gave an opportunity for more accurate evaluation of any serum that might be produced.

Finger and Landsteiner treated 2 patients presenting chancres, with serum from syphilitic apes, having first excised the chancre in one case and both chancre and inguinal nodes in the other. In spite of this treatment secondary manifestations developed in these patients in the usual manner. Neisser carried out a large series of experiments which had for their purpose the demonstration of the possibility of passive immunization against syphilis. It may be said at once that they all yielded negative results. He inoculated horses, cattle, sheep, and monkeys with both living and killed virus from both human and animal sources and then tested the serum of these animals as regards (1) its treponemicidal power *in vitro*, (2) its protective power *in vivo* in apes when injected locally at the site of inoculation and when administered subcutaneously or intravenously, and (3) its curative power in apes when given intravenously or subcutaneously after infection had been established. In no instance was there any evidence that the serum exerted any effect upon the course of the disease or modified the virus *in vitro*.

The results in rabbits have been equally fruitless Truffi (82) attempted to protect rabbits against syphilitic infection by treating them with serum from other rabbits that had proved to be immune to a second infection with syphilitic virus In spite of treatment prior to inoculation the test animals proved to be as susceptible as normal animals to virus introduced into the subscrotal tissue Uhlenhuth and Mulzer found that the serum of rabbits that had received several injections of living syphilitic virus was totally incapable of modifying the course of syphilis in other rabbits either when given at the time of inoculation or after the appearance of clinical manifestations of infection Moreover, such serum was incapable of agglutinating treponemes or of forming a precipitate when brought into contact with an emulsion of these organisms Nakano (89) injected rabbits intravenously with cultures of treponemes and found that the serum of these animals, although it possessed some agglutinating power for the organisms in the culture, had no protective power *in vivo* and failed to exert any beneficial action when administered to syphilitic rabbits, either intravenously or locally at the site of the syphilitic process \*

The question as to whether or not immunity to syphilis can be transmitted to offspring deserves consideration at this point For a time it was thought that such might be the case and, as is well known, the principle was expressed in the form of a law (Profeta's law), to the effect that the offspring of a syphilitic woman might nurse an infected woman with impunity and never show signs of syphilis The advent of the Wassermann reaction served to show that these supposedly immune children were in reality themselves syphilitic and that their immunity was presumably dependent upon their own infection and not upon a passive transfer of immune bodies from the mother Nobody has yet succeeded in bringing forward any convincing evidence that the offspring of syphilitic parents are immune to syphilis and at the same time entirely free of syphilitic infection Nevertheless, the idea has been entertained in some quarters that the refractory state which develops in syphilitic individuals may in

\* Jáuregui and Lanceotti (161, 162) have reported that they have obtained an immune serum from lambs which, when administered to animals of this species infected with syphilis or to syphilitic patients, exerts a marked beneficial effect upon the course of the disease



part be transmitted from parent to child, and that in this way in the course of time the human race may gradually build up a heightened resistance to the disease. Some of those who have been attracted to this hypothesis have contended, in support of it, that the course of syphilis is milder now than it was several centuries ago. Neisser was unwilling to accept such a conclusion, however. He thought that the milder course of syphilis nowadays may be referable to a number of other factors, such as more precise differentiation of syphilis from other diseases, better individual hygiene, and better therapeutics. Moreover, he pointed out that when syphilis makes its appearance in virgin soil, so to speak, it does not always pursue a malignant course. Furthermore, in Neisser's opinion, in lands where the disease has been prevalent for years the course of the disease is not appreciably different from that in countries where it is not so prevalent. On the whole, then, there is little or no evidence to show that acquired resistance to syphilitic infection can be transmitted through inheritance, just as there is at present no satisfactory evidence to show that passive immunization can be accomplished or the course of an established infection altered by the administration of serum from immune persons or animals.

#### ANTIBODIES IN SYPHILIS

Attempts have naturally been made to demonstrate in the blood serum of syphilitic patients or of animals that have been experimentally infected with syphilis, the presence of antibodies analogous to those that have been found in other infections. The reports that have thus far appeared have yielded rather divergent results so that the matter is in a somewhat confused state at the present time.

*Agglutinins. a Man* Numerous attempts have been made to demonstrate agglutinins for *T pallidum* in the serum of patients with syphilis. Hoffman and v Prowazek (95) exposed emulsions of treponemes to the action of serum from patients with untreated syphilis of 6 to 8 months duration and thought they observed some tendency on the part of the organisms to undergo agglomeration and loss of motility. They expressed themselves in a very conservative fashion, however, concerning this phenomenon and one gets the idea that it was not a particularly striking one. Zabolotny and Maslakowetz

(96) obtained analogous results but Landsteiner and Mucha (97) failed to obtain any evidence of agglutinating power on the part of the serum of patients with syphilis. These investigators, however, observed a tendency toward agglutination in preparations of material from human syphilitic lesions and suggested that this phenomenon might be due to the formation of agglutinins locally at the site of the syphilitic process although no such agglutinins were observed in the serum of the same patients. Uhlenhuth and Mulzer (98) were unsuccessful in demonstrating in the serum of patients with syphilis, agglutinins for treponemes derived from syphilitic lesions. On the other hand, Touraine (99), using the microscopic method, concluded that he was able to demonstrate agglutinins for tissue treponemes in the serum of a number of syphilitics with varying manifestations of the disease, and was of the opinion that the procedure might be utilized for the diagnosis of syphilis. Kissmeyer (100) found that the serum of some syphilitic patients agglutinated cultures of treponemes in higher dilution than did the serum of normal persons and Kolmer, Broadwell and Matsunami (101) had essentially the same experience. On the other hand, Arnheim (102) obtained negative results and Zinsser, Hopkins and McBurney (103) found that the serum of syphilitic patients did not agglutinate cultures of treponemes in an appreciably higher dilution than did normal human serum, and did not agglutinate treponemes obtained from syphilitic lesions. In their opinion agglutination could not be employed as a diagnostic measure. Siemens and Blum (104) extracted the skin of paretics and sought to demonstrate the presence of treponeme-agglutinating substances in these extracts but were unsuccessful.

*b Rabbit* Uhlenhuth and Mulzer (98) were unable to obtain any evidence of agglutinins in the serum of rabbits experimentally infected with syphilis. On the other hand, Zinsser, Hopkins and McBurney (103) found that the serum of syphilitic rabbits agglutinated cultures of treponemes in dilutions of 1:25 to 1:50 but did not exert any agglutinating or immobilizing effect upon virulent treponemes from rabbit lesions. Blum (105) also worked with suspensions of treponemes obtained from syphilitic lesions in the rabbit and found that the serum of syphilitic rabbits agglutinated these organisms at times in dilutions as high as 1:100, while only occasionally did normal rabbit serum

agglutinate them and never in dilutions greater than 1:10. In his experience the occurrence of agglutinins seemed to be dependent upon the duration of the infection and the extent of the clinical manifestations. Almost all workers in this field have reported the production of agglutinins in the serum of rabbits after the intravenous injection of cultures of these organisms, the maximum titer varying with different observers [Nakano, 1:60 (89), Kolmer, 1:1280 (106), Zinsser and Hopkins, 1:4000 (107), Kissmeyer, 1:20,000 (100), Noguchi and Akatsu, 0.000025 cc (108)]. Zinsser, Hopkins, and McBurney (109) made the important observation that a serum which would agglutinate culture treponemes in a dilution of 1:4000 would not agglutinate the same strain when the organisms were obtained from syphilitic lesions in the rabbit. For some unexplained reason the virulent organisms could not be affected by the agglutinating serum, although the culture treponemes were readily agglutinable. By means of cross agglutination and absorption experiments these investigators showed that treponemes from different sources were "related in group reactions."

*Treponemicidal substances* Finger and Landsteiner inoculated a series of 12 apes with mixtures of virus and serum from patients in various stages of syphilis, the serum-virus mixture being allowed to stand for  $\frac{1}{2}$  hour before inoculation. In each animal a lesion developed at the site of inoculation indicating that the serum did not possess a high degree of treponemicidal activity. Nakano (89) was unable to demonstrate the presence of treponemicidal substances in the serum of rabbits immunized with cultures of treponemes when he exposed the treponemes to the action of the serum in the test tube. When he injected the immune serum and treponemes into the peritoneal cavity of guinea pigs, however, lysis of the organisms took place promptly. Control inoculations with normal rabbit serum under the same conditions did not bring about lysis nor did the serum of patients with early or late syphilis. So far as the writer is aware Nakano is the only investigator who has reported the occurrence of the Pfeiffer phenomenon in association with the serum of animals immunized with *Treponema pallidum*.

Zinsser and Hopkins (110) found that the serum of rabbits and of sheep immunized with cultures of treponemes exerted a treponemici-

dal action upon cultures of treponemes *in vitro*. According to them the treponemicidal activity was abolished by heating at  $56^{\circ}\text{C}$ , but could be reestablished by the addition of fresh normal serum. This observation would, of course, bring the treponemicidal substance or substances into line with other well known antibodies. According to these investigators the property was not strain specific and normal serum was found by them to possess a slight degree of treponemicidal activity although by no means to the same extent as did the serum of immunized animals. Later Zinsser, Hopkins and McBurney (109) showed that the treponemicidal activity of the serum of the immunized animals was not effective against virulent treponemes derived from syphilitic lesions in the rabbit, although it retained its activity for culture treponemes. Noguchi and Akatsu (108) succeeded in demonstrating the presence of treponemicidal substances in the serum of rabbits immunized with cultures by intravenous injections repeated over many weeks. In some instances amounts of serum as small as 0.0003 cc were, in their hands, capable of destroying the treponemes in the test tube. The addition of complement was found to enhance the treponemicidal activity appreciably. Microscopical examination of the contents of the tubes in which the reaction took place revealed striking changes in the morphology of the treponemes. The serum of a syphilitic rabbit was found to exhibit treponemicidal activity in amounts greater than 0.03 cc, whereas 0.1 cc of normal rabbit serum exerted only slight restraint of growth.

Eberson (111) investigated the treponemicidal activity of serum from human beings in various stages of syphilis and found no evidence of such in 7 patients with recent infections. On the other hand, the serum of 18 patients with latent syphilis in whom the infection was thought to have occurred at a more remote time was found to possess treponemicidal power for virulent treponemes derived from rabbit lesions. In his experiments the serum was allowed to act upon the virus in the test tube, the mixture being subsequently inoculated intratesticularly into rabbits. Treponemicidal activity did not go hand in hand with a positive Wassermann reaction since it was observed in several specimens of serum obtained from treated patients whose Wassermann reaction was negative. The serum of syphilitic rabbits was found to possess treponemicidal power when the animal from

which the blood was obtained had had its infection for 6 months or more, but treponemicidal activity could not be demonstrated in the serum of rabbits whose infection was of shorter duration. It should be noted that in Eberson's experiments the serum was preserved for some time and was heated at  $54^{\circ}\text{C}$  for 20 minutes before testing, also that he did not apparently find it necessary, as had Zinsser and his coworkers, to add complement in order to bring about the reaction. It is, of course, conceivable that the small amount of serum or tissue juice in which the treponemes were suspended was sufficient to supply any complement that may have been necessary to ensure the success of the reaction. So far as the writer is aware these experiments are the first in which treponemicidal activity of the serum of syphilitic patients or animals for virulent treponemes is described. In view of the significance of such a finding it is to be hoped that confirmation will be forthcoming.

*Precipitins* Fornet and his collaborators (112) sought to demonstrate the presence of precipitins in the serum of patients with syphilis (particularly cases of paresis and tabes), and for this purpose used as antigen the serum of other syphilitics who possessed manifest lesions. They assumed that because such patients exhibited active manifest lesions their blood serum would be more apt to contain precipitinogen than the serum of syphilitics without obvious lesions, hence could be used as antigen. They found that when the serum of such patients was allowed to come in contact with the serum of other patients, whose infection was latent, a precipitate was formed in a large proportion of the cases. Normal serum did not give a precipitate under the same conditions. The formation of a precipitate under these circumstances was regarded by these investigators as an example of a true antigen-antibody reaction, and they thought it indicated the formation of specific precipitins in the body of the syphilitic individual. L. Michaelis (113) at the same time extracted the liver of a syphilitic fetus with salt solution and found that when this extract was brought in contact with the serum of a patient with hereditary syphilis a precipitate was formed. He expressed the thought that the reaction might ultimately supplant the Wassermann test as a diagnostic procedure, a rather prophetic remark in view of the apparently increasing popularity of precipitin tests as diagnostic

procedures in syphilis Jacobsthal (114) later found that when the ordinary Wassermann "antigens" were brought in contact with serum from patients with syphilis a precipitate was formed which was visible under the microscope if dark field illumination were used. It was at first supposed that these precipitin reactions represented specific antigen-antibody reactions but this notion was soon abandoned. Despite this fact interest in the phenomenon was maintained and numerous attempts were made to modify the reaction so as to be able to utilize it for the diagnosis of syphilis. The names most prominently associated with this work are those of Bruck and Hidaka (115), Hecht (116), Meinicke (117), Sachs and Georgi (118), and Dreyer and Ward (119) abroad, and Kahn (120) in this country. Already a considerable literature on the subject has accumulated. The modification advocated by Kahn has been enthusiastically received in some quarters, where it has been substituted for the Wassermann reaction as a routine procedure in the diagnosis of syphilis. The test is, of course, an empirical one, and not a true antigen-antibody reaction in the strict sense of the term. Takenaka (121) has recently reported the occurrence of positive Sachs-Georgi reactions in the serum of syphilitic rabbits and finds that this test parallels the Wassermann test very closely in these animals. Specific precipitins for cultures of *Treponema pallidum* in the serum of patients with syphilis have not as yet been encountered although they were sought for by Arnheim (102). In Nakano's hands rabbits immunized with cultures of *T. pallidum* failed to develop precipitins in their blood for these organisms (89).

*Complement-fixing substances* As is well known, the original complement-fixation reaction reported by Wassermann, Neisser and Bruck represented an attempt to demonstrate, in the serum of patients with syphilis, the presence of complement-binding substances for *Treponema pallidum*, presumably produced as a result of invasion of the body by the latter. In the absence of cultures of the organism resort was had to extracts of livers of syphilitic fetuses for antigens, since these organs were known to contain an abundance of treponemes. In spite of the heterogeneous mixture of chemical substances which such extracts must have contained, Wassermann's original conception was that the reaction represented a true antigen-antibody reaction. This idea had to be abandoned later when it was found that extracts of normal

organs would take the place of extracts of syphilitic fetal livers as "antigens" in the test, although for some years Wassermann clung to the idea that there was an element of strict antigen-antibody reaction in connection with the test

As everyone knows, the literature that has accumulated in connection with the Wassermann reaction has become so enormous that it is almost beyond the capacity of any single individual to review it adequately, and this is scarcely the place to enter into a discussion of the various views that have been proposed to explain its nature. The consensus of opinion at the present time seems to be that it is a physical-chemical reaction connected in some way with the lipoids and syphilitic infection. Just why the serum of patients with syphilis and yaws should give this reaction and the serum of patients with other conditions should not give it, except in unusual instances, is not by any means clear. It should be mentioned at this point that recent reports from Germany suggest that there is an element of true antigen-antibody reaction in the Wassermann test (122). It is much too early to pass final judgment upon these most recent contributions to the nature of this intriguing test but it would be interesting indeed if the Wassermann reaction, after having been relegated to the limbo of empiric tests for so many years, should after all be haled back to the select company of strictly specific antigen-antibody reactions.

It may be noted in passing that the recent work of Takenaka (123), Wakerlin and Carroll (124), and Kemp, Chesney and Poole (125) indicates that with a prescribed technique syphilitic rabbits give positive Wassermann reactions during the period of manifest lesions and normal rabbits give negative reactions. This is not in accord with the traditional view prevalent in Germany, to the effect that the reaction cannot be relied upon in rabbits, but supports the earlier observations of Nichols (126).

*Opsonins* So far as the author is aware, opsonins for *Treponema pallidum* have not been demonstrated in the serum of patients with syphilis. Nor has it been clearly shown that phagocytosis plays an important rôle in the mechanism of resistance to syphilitic infection. It is true that examples of phagocytosis of treponemes in syphilitic lesions have been described by Ehrmann (127) and Levaditi (128) but the experiments of Zinsser and Hopkins (129) with mice inoculated

intraperitoneally with *Treponema pallidum* would make it appear as if phagocytosis were of little or no importance in natural resistance to syphilitic infection. Bergel (130) has recently reported results which are in direct conflict with those of Zimsser and Hopkins. According to the former, phagocytosis of treponemes by lymphocytes and large mononuclear cells can be demonstrated to take place in the peritoneal cavity of rabbits, guinea pigs and mice, when these species are inoculated intraperitoneally with material containing treponemes. It is by no means easy to form a judgment as to the rôle played by phagocytosis in natural or acquired resistance to syphilitic infection because of the technical difficulties involved in the problem, and further studies along this line are urgently needed.

*Cutaneous hypersensitiveness* Following the discovery of *Treponema pallidum* numerous attempts were made to extract from syphilitic tissue substances which, when injected into the skin of patients with syphilis, would provoke reactions of an allergic nature that would be specific and perhaps prove to be of diagnostic value. For the most part the livers of syphilitic fetuses constituted the source of this material. It is scarcely necessary to refer to the earlier work in great detail since the reports were very conflicting, as might indeed be expected in view of the varying chemical constitution of the mixtures obtained by extracting syphilitic tissue. While rather favorable results were reported by Meirrowsky (131), Nicholas, Favre and Gauthier (132), and Nakano (133), negative or only slightly favorable results were obtained by Ciuffo (134), Jadassohn (135), Bertin and Le Bruyant (136) and Fontana (137).

The cultivation of *Treponema pallidum* in the test tube, however, offered greater prospect of success in this undertaking and led Noguchi to prepare an extract ("luetin") from cultures of this organism to be used as a skin test in the diagnosis of syphilis (138). Preliminary experiments with rabbits encouraged him to apply the test to human beings and several investigators beside himself reported favorable results obtained with the test, but the procedure has not made great headway as a means of diagnosing the presence of syphilitic infection, perhaps because of the fact that the Wassermann reaction has proved to be a more potent aid. The demonstration by Sherrick (139) that the administration of potassium iodide to patients with conditions



other than syphilis will frequently cause such patients to give a positive luetin reaction makes the test of limited value for diagnostic purposes. Nevertheless, Noguchi's work suggests that late in the course of syphilis there occurs a cutaneous hypersensitiveness to extracts of cultures of *Treponema pallidum*. Nakano (133) found that filtrates of cultures of this organism gave a higher percentage of positive skin reactions in syphilitic patients than did extracts of the same cultures, but that extracts of syphilitic livers gave the highest percentage of positive reactions. Nakano, furthermore, was able to show that the subcutaneous injection, in 2 human volunteers, of an extract of syphilitic liver, was capable of inducing in these individuals cutaneous hypersensitiveness to the same extracts injected intracutaneously. Similar results were obtained by this investigator in guinea pigs and rabbits. It may be noted in passing that Uhlenhuth and Mulzer were unable to obtain any evidence of the existence, in syphilitic rabbits, of cutaneous hypersensitiveness to syphilitic virus.

Attempts have not been lacking to demonstrate the presence, in the serum of syphilitic animals, of substances which, when transferred to guinea pigs, would passively sensitize these animals to material containing treponemes. Uhlenhuth and Mulzer injected guinea pigs intraperitoneally with 3 to 5 cc. of serum of syphilitic rabbits and inoculated them intravenously on the following day with approximately 1 cc. of an emulsion of syphilitic rabbits' testis. None of the guinea pigs showed anaphylactic symptoms. Nakano (133) apparently was able to sensitize guinea pigs by the intraperitoneal injection of extracts of syphilitic livers and subsequently, to produce characteristic anaphylactic shock by the intravenous injection of the same extracts. Extracts of normal livers did not shock the animals. Evidence of the formation of anaphylatoxin in mixtures of syphilitic serum and extracts of syphilitic livers, in mixtures of cultures and guinea pig serum, and in mixtures of extracts of syphilitic tissue and guinea pig serum, was also obtained by this investigator.

*Summary* It is clear from the foregoing analysis of the attempts to demonstrate the occurrence of specific antibodies in the course of syphilitic infection, that the subject is far from being settled. While one or another investigator has convinced himself that this or that kind of antibody can be shown to develop in patients with syphilis,

there are many conflicting reports. Nor is it by any means clear that the so-called antibodies that have been demonstrated have, in reality, anything to do with recovery from syphilitic infection or with acquired or natural resistance to the disease. It does seem definitely established that by the use of suitable procedures certain kinds of antibodies can be produced in the rabbit but when the very animal possessing these antibodies in its serum is found to be as susceptible to infection with potent virus as is a normal animal, one can scarcely escape the conclusion that such antibodies are of little value as a means of protection for the animal.

#### IMMUNOLOGICAL RELATIONSHIP OF SYPHILIS TO OTHER INFECTIONS DUE TO TREPONEMES

It may be of interest, before discussing the nature of immunity in syphilis, to consider the immunological relationship of this infection to those other infections (both of man and rabbits), which are caused by treponemes indistinguishable from *T pallidum*. At the present time, as is well known, there is one such infection occurring in man (yaws), and one in rabbits (venereal spirochetosis), and it is generally conceded to be impossible, on morphological grounds, to differentiate the microorganisms causing these diseases from that causing syphilis.

#### *Yaws*

It is not within the province of this review to discuss in detail the question of the identity of yaws and syphilis. Considerable discussion has arisen in regard to it and there is as yet no unanimity of opinion although perhaps the majority of observers regard the conditions as separate disease entities. Leaving aside, then, the question of identity, is there any evidence that an attack of yaws is capable of protecting an individual against an attack of syphilis? According to Castellani and Chalmers (140) yaws patients are not immune to syphilis and vice versa. They cite the earlier observation of Char-  
lous (141) who inoculated a yaws patient with syphilitic virus and produced a characteristic attack of syphilis. At the time of inoculation this patient presented a yaws lesion and 4 weeks later there appeared at the site of inoculation (breast in this case) a typical indurated

TABLE 6  
*Cross inoculations of monkeys with yaws and syphilis*

AUTHOR	ANIMAL	FIRST INOCULATION	INCUBATION PERIOD	INTERVAL BETWEEN INOCULATIONS	SECOND INOCULATION	RESULT	INCUBATION PERIOD
Neisser, Baermann and Halberstadter	Mac cyn.	Yaws	46	days	Syphilis	Positive	21
	Mac nig	Syphilis	26	41	Yaws	Positive	34
Halberstadter	Mac cyn	Yaws	49	73	Syphilis	Positive	22
	Mac nem	Syphilis	36	296	Yaws	Positive	46
	Mac cyn	Syphilis	52	58	Yaws	Positive	42
Castellani	Mac pil	Yaws	?	About 136	Syphilis	Positive	26
	Mac cyn	Yaws	32	101	Syphilis	Positive	42
Levaditi and Nattan-Larier	Mac rhes	Syphilis	15	74	Yaws	Negative	
	Mac cyn	Syphilis	20	91	Yaws	Negative	
	Mac cyn	Syphilis	22	91	Yaws	Negative	
	Mac rhes.	Syphilis	19	95	Yaws	Negative	
	Bon chun	Syphilis	28	110	Yaws	Negative	

tained by others in syphilitic rabbits when heterologous strains of *T pallidum* were used for the second inoculation (see table 2) Voegtlin and Dyer (70) have also recently adduced evidence to show that treated syphilitic rabbits which are refractory to a second inoculation with syphilis are refractory to inoculation with yaws virus Kolle (51) found that 7 syphilitic rabbits were all refractory to infection with yaws virus, while of 15 rabbits infected with yaws, 9, or 60 per cent, could be successfully infected with syphilis In his experiments at least 120 days elapsed between inoculations

Of interest is a recent experiment of Jahnel and Lange (150) These investigators inoculated 4 paretics with yaws virus which had been propagated in rabbits' testes In none of the patients did a lesion develop although the virus was rubbed into scarified areas of the skin, injected intracutaneously and bits of infected rabbit testis were implanted in the deeper layers of the skin That failure of the paretics to show lesions could not be attributed to avirulent virus was demonstrated by the fact that a normal individual inoculated as a control with the same material developed yaws lesions

*Summary* There is some evidence, of an epidemiologic nature, that in man infection with yaws protects against syphilis, although instances of both infections occurring simultaneously in the same individual have been reported The evidence obtained from experiments with monkeys is somewhat conflicting, but recent work with rabbits suggests that there is a close biological relationship between the etiologic agents of the two diseases If it is true that an attack of yaws is capable of protecting man against syphilis one cannot help wondering if it might not be possible to protect human beings against syphilis by systematic inoculation with yaws virus, even to the extent of producing a mild attack of the latter Perhaps the tropics will yet see a new Jenner If there is anything in the idea that yaws protects against syphilis, one might be justified in raising the question as to whether campaigns to eradicate yaws are after all of real value in communities exposed to syphilis Which would be better, yaws in childhood with concomitant immunity to syphilis later in life, or no yaws and susceptibility to syphilis?

*Venereal spirochetosis of rabbits*

This infection has of late attracted considerable attention because of the possibility of confusing it with experimental syphilis in the rabbit. It is an infection indigenous to rabbits, manifesting itself as a localized chronic dermatitis of the genitalia and anus. The lesions are superficial, scaly, and entirely without induration, and can scarcely be mistaken for syphilitic lesions. The disease appears to be more common in Europe than in America. It is transmissible from rabbit to rabbit by sexual intercourse, whereas *T pallidum* infection in rabbits is not transmissible by that method.<sup>7</sup> The condition is universally held to be due to infection with a variety of treponeme (*T cuniculi*) which is morphologically indistinguishable from *T pallidum*. The experiments of Kolle, Ruppert and Mobus (151) demonstrate conclusively that there is no evidence of immunologic relationship between *T pallidum* and this organism. Rabbits infected with the former are susceptible to infection with the latter and vice versa.

## NATURE OF IMMUNITY IN SYPHILIS

The fact that a syphilitic individual, whether man, monkey or rabbit, acquires during the course of his disease a resistance of a rather high order to a second syphilitic infection, although it is impossible to confer this resistant state upon a representative of any of these species by any known method of immunization at the present time, has naturally led to much speculation as to the nature of this acquired resistance and the mechanism of its production. Obviously the circulating blood would be at once considered, particularly in view of the fact that in relapsing fever recovery can be shown to be accompanied by the appearance in the blood serum of spirocheticidal substances which are capable of exerting their action in the test tube. The proponents of the humoral theory of immunity in syphilis have, however, found but scant support amongst the known facts. There is really very little evidence, apart from the work of Eberson, to indicate that there are

<sup>7</sup> Marie, Levaditi and Banu (152) reported the transmission of their so-called "neurotropic" virus of syphilis from rabbit to rabbit by sexual intercourse but most workers in experimental syphilis are of the opinion that they confused *T pallidum* with *T cuniculi*, and that in reality it was venereal spirochetosis of rabbits that was transferred and not syphilis.

circulating antihodies in syphilis which play a rôle in the mechanism of acquired resistance to this infection. While there have been many references to the Wassermann reaction as indicating the presence of a circulating antibody in the blood, strictly speaking there is no evidence at present to show that the unknown substance or condition which gives rise to this reaction in the course of syphilis is at all concerned with the mechanism of recovery from or resistance to, this infection.

The general failure of investigators to demonstrate, in the blood serum of syphilitic patients or animals experimentally infected, the presence of substances antagonistic to virulent treponemes, has naturally directed attention away from the blood and toward the tissues as the seat of the resistance. There can be no question but that the tissues of the syphilitic are profoundly altered from those of the normal in their capacity to react to syphilitic virus introduced from without. They can be shown to be highly refractory to such exogenous virus and, in the great majority of instances, the virus is apparently completely disposed of without the development of gross signs of inflammation when it is introduced into the skin or subcutaneous tissue of syphilitic patients. Neisser was unwilling to apply the term "immunity" to this resistant state, however, for, as has been previously outlined, his own experimental work led him to conclude that it was dependent upon the persistence of foci of syphilitic infection in the body.<sup>\*</sup> What others had regarded as true immunity Neisser contended was only an acquired inability of the skin to react to new virus introduced from without. According to him the condition might be regarded as merely one of acquired indifference to syphilitic virus, without the factor of protection for the host being necessarily implied. For this condition he proposed the term "anergy." He regarded the anergic state as relative and not absolute, and had the idea that it developed gradually and perhaps not at a uniform rate in all the tissues. He pointed out that it appears at about the time the Wassermann reaction becomes positive and he thought that it probably diminished in the later periods of the disease.

Kraus and Volk (22) proposed the view that the resistant state that

<sup>\*</sup> This type of resistance was designated "Hals immunität" by Ehrlich. Recently Kolle has spoken of it as "Infektionsimmunität."

develops during the course of syphilis might be conferred upon certain tissue groups, the skin for example, and not upon others, in other words, that it was regional in distribution and perhaps not general. These workers found support for this conception of regional immunity in the immunological relationships that have been found to hold in the case of vaccinia. They called attention to the work of von Prowazek (153) and of Jurgens (154), which they were able to confirm, to the effect that inoculation of one cornea of a rabbit with vaccine virus did not protect the skin or the opposite cornea against subsequent inoculation with the same virus. They also showed that cutaneous inoculation of apes with vaccine virus and the production of a pustule did not protect the cornea against subsequent inoculation. These experiments offer strong support for the conception of a regional immunity in the case of vaccinia and present an attractive explanation by analogy for what has been observed in syphilis.

Subsequent reinoculation experiments by Tomaszewski with rabbits, to which allusion has already been made, may be regarded as offering support for this conception of regional tissue immunity in syphilis. It will be remembered that this investigator found that rabbits with pre-existing syphilitic orchitis could be successfully infected a second time by corneal inoculation, whereas the skin of such animals was refractory to the introduction of new virus. He found also that rabbits which had been inoculated in the cornea and in which keratitis had developed could be successfully inoculated in the testis. On the other hand, Uhlenhuth and Mulzer obtained directly opposite results.

Kraus was of the opinion that the skin participated in the immune process while the internal organs did not. This independent sharing by various tissues or organs in the immunizing process in syphilis finds support in the clinical observation that patients with tabes dorsalis or paresis rarely show syphilitic skin or bone lesions and rarely give a history of extensive eruptions. Neisser, however, was unable to admit that there was any evidence, from either the clinical or experimental standpoint, that a reciprocal relationship existed between immunity of the skin on the one hand and immunity of the internal organs on the other.

The conception that the resistant state which develops in individuals

during the course of syphilitic infection is not distributed uniformly throughout the body but that various tissue groups may share in it to an unequal extent under certain conditions has been strengthened by the work of Brown and Pearce (155). These investigators, working with rabbits, have come to the conclusion that the character of the initial response of the animal to syphilitic infection will determine the subsequent course of the disease so far as the evolution of generalized macroscopic lesions (detectable during life) is concerned, also that the occurrence of reactions in certain tissue groups tends to influence the occurrence of reactions in other tissue groups. The observations that they have been able to make have led them to formulate two laws which they speak of as the "law of inverse proportions" and the "law of progression or sequence." According to the former of these two laws the course of syphilis in the rabbit is in inverse ratio to the extent and intensity of the initial local reaction. In other words, in animals with marked outspoken primary reactions the subsequent course of the infection (number and extent of generalized lesions), is milder than in those animals in which the primary response is relatively slight or is suppressed by artificial means. Their second law, the law of progression or sequence, is based upon the observation that when syphilis is allowed to run its course undisturbed in the rabbit there tends to be an orderly development of metastatic lesions, those involving one tissue group tending to make their appearance before those involving other tissue groups. It is the conception of these investigators that this state of affairs reflects a "natural order of susceptibility and of involvement," and they consider that reactions taking place in one group of tissues may give rise to protective influences which are imparted to other groups of tissues, again in an orderly fashion. It is clear that this conception implies that the resistant state which develops during the course of syphilis is at least unequally shared by certain tissues, and it seems not unlikely that this inequality of participation in the immune reaction may explain the subsequent course of the disease in any given individual.

Largely upon the basis of his own work, Zinsser (4) has suggested that the refractory state which develops during the course of syphilitic infection may be the expression of a local immunity developing *in situ* wherever the microorganisms happen to lodge and set up a reac-



tion Here then we have a narrower conception of syphilitic immunity than that of the regional idea advanced by Kraus The evidence upon which Zinsser bases his proposal was derived from experiments by himself and co-workers upon a series of rabbits These investigators found that "the opposite testis can be successfully inoculated before, during or after, the existence of a testicular lesion on one side, but that reinoculation of the same testis which had apparently returned to normal, at periods ranging from 6 weeks to one year, was not often successful" Study of the protocols of these experiments reveals the fact that in the instances where Zinsser and his collaborators obtained undoubted reinfections, heterologous strains of treponemes were used for reinoculation, whereas when homologous strains were used no reinfections were obtained Because of the use, by these workers, of heterologous strains for reinoculation, and because of the now well established fact that in the rabbit the acquired resistance to syphilitic infection is more effective against homologous than against heterologous strains of treponemes, one is justified in being cautious before accepting the interpretation that Zinsser has put upon his experiments

Chesney and Kemp (49) found that the opposite uninvolved testis of syphilitic rabbits treated late in the course of their infection was just as refractory to a second inoculation with homologous strains as a testis which had been the seat of a syphilitic inflammatory reaction prior to treatment Moreover, in an experiment the report of which is now in course of publication these same investigators were able to show that granulating wounds in immune rabbits share in the anergic state to some, although not quite the same extent as do testes which were formerly diseased In a series of 16 rabbits inoculated intratesticularly and treated late in the course of the disease, at a time when from previous experience one could be certain that they would be refractory to a second intratesticular inoculation, second inoculations were performed by applying the virus to a granulating wound (14 days old) on the back of the animal In only one of the 16 animals did a lesion (chancre) develop at the site of inoculation, in the remaining 15 no lesion made its appearance but in at least 7 of these 15 there was evidence that infection had taken place and that dissemination of the virus had occurred Since in this experiment the wounds were

made after thorough treatment and the granulation tissue represented new tissue which could scarcely have been exposed to invasion by treponemes until the time of the second inoculation, this experiment would tend to indicate that in order for tissue (of rabbits) to acquire the anergic state toward treponemes, it is not necessary that there be previous infection of that tissue by the organisms. Apparently in the rabbit, at least, the acquired refractory state or anergy or immunity, call it what you will, is a property which may be imparted to newly-formed granulation tissue but is not absolute, since under the conditions of the experiment systemic infection of some of the animals occurred even though no lesion developed at the site of inoculation.

This last fact, that syphilitic animals that have been treated can be successfully infected a second time without the development of any lesion at the site of reinoculation, has been substantiated in several experiments performed by the writer in association with Kemp, and it suggests that in immune animals the circulating blood does not share in the resistant state to the same extent as the tissues at the site of reinoculation. If, as these investigators have demonstrated, the resistant state can be conferred upon newly-formed granulation tissue and if, in addition, it can be shown that there is no humoral factor operating in syphilitic immunity, one may perhaps conclude that the resistant state is confined to the cells and can be transmitted to successive generations of new cells. On the whole, there is more evidence in favor of the view that the mechanism of immunity in syphilis is more closely related to the cells than to the blood, although neither of these factors can be ruled out at the present time and it is not unlikely that both are involved.

It might be supposed that phagocytosis would play a rôle in the mechanism of acquired immunity in syphilis but thus far little evidence has been forthcoming to indicate that it is of any significance, either in natural or acquired resistance to this infection. Little is known of the extent to which it enters into the process of healing of the initial manifestations of the disease. While both Ehrmann and Levaditi claim to have observed in stained sections examples of what they regarded as phagocytosis of treponemes, and Bergel attaches great importance to the process, the experiments of Zinsser and Hopkins on mice, on the other hand, make it seem likely that it is not of

major importance as a defensive mechanism for animals not inherently susceptible to syphilitic infection. Moreover, the ease with which granulating wounds of normal rabbits can be inoculated with virulent strains of *T pallidum*, as demonstrated by Chesney and Kemp (156), does not lend support to the idea that the phagocytic cells of the rabbit are particularly active against living virulent treponemes. Nevertheless, the reservation should be made that in the immune animal phagocytosis may have a much more important part in the defensive mechanism than can be determined at the present time with the methods at our disposal.

This phase of the subject should not be dismissed without calling attention once more to the observations of Bergel (130). This investigator has come to the conclusion that the lymphocytes and macrophages are of prime importance in the destruction of treponemes in the body of the host. He is convinced that phagocytosis of these organisms by these particular cells takes place with great frequency in syphilitic infections, and he claims to have observed in fresh specimens of material from syphilitic lesions the engulfing of living, actively motile specimens of *T pallidum* by lymphocytes and macrophages and their subsequent dissolution within the cell. He is of the opinion that both extra- and intracellular lysis of treponemes is brought about through the agency of lipolytic enzymes which the lymphocytes are capable of elaborating and discharging into the surrounding medium. His conception of the defensive mechanism in syphilis, then, is that it is in large part a reaction taking place between the lipoidal treponemes on the one hand, and lipolytic enzymes evolved by the lymphocytes on the other, with destruction of the former. It is clear from a perusal of Bergel's communication that much of his hypothesis rests upon the interpretation of stained preparations checked by examination of fresh preparations observed by the dark field method. Because of the dangers of misinterpretation of stained specimens, opinion as to the views of Bergel must be guarded for the time being, nevertheless, the conception is new and offers the possibility of a fresh line of attack.

If it is an established fact that human beings with syphilis acquire, early in the course of their disease, a resistance to new infection from without, to the extent that the skin is wholly refractory to relatively large amounts of foreign virus introduced upon a scarified area, how

can one reconcile with this state of affairs the fact that such individuals may, and not infrequently do, continue to show lesions on their skin, mucous membranes and elsewhere, caused by their own virus coming from within? Here apparently is a paradox—acquired resistance to exogenous virus but continuing susceptibility to endogenous virus. This peculiar situation has for years been a matter of keen interest to students of syphilis. As long ago as 1884 Neisser (157) called attention to it and in the intervening years several hypotheses have been offered in explanation.

It has been suggested that the superficial layers of the skin acquire the refractory state in advance of the deeper layers so that the host is protected against outside virus before he is protected against that coming from within. Against this view is the well known fact that secondary lesions of syphilis do eventually involve the most superficial layers of the integument. Another view that has been proposed is that from time to time there occur fluctuations in the refractory state which permit successive crops of treponemes to be engendered, these in turn producing lesions. It must be admitted that the existence of such fluctuations has not been proved and it seems unlikely that they occur during the early stages of the disease at any rate. It is conceivable that the apparent paradox might be explained upon the basis of Zinsser's theory, namely that the resistant state is a local phenomenon dependent upon direct invasion of the tissues by the parasites. According to this conception if lesions developed subsequently in a given tissue or organ it would be because that particular locality had not been invaded at the time of the first dissemination of the treponemes or at any rate had not been the seat of an inflammatory reaction. Still another hypothesis that might explain the observed facts would be the supposition that *Treponema pallidum* possesses a complicated life cycle during the course of which it enters phases which are more virulent or more resistant against the body defenses. Nothing definite is known of a life cycle for this organism in which the parasite takes on a new or different morphology from that with which we are now familiar, although at least one author, McDonagh, (158) has been insistent in his claims that there is such a complex cycle, and not a few others have toyed with the idea.

The hypothesis to which both Neisser and Levaditi lend their adher-

ence, in order to explain the apparent paradox, holds that the treponemes develop a resistance against the treponemicidal agents of the host, that the former themselves become immunized as it were and in this manner are able to resist a defensive mechanism which is fully capable of dealing with and destroying foreign virus. One may conceive of a balance being struck between the host and the parasite, a mutual immunization as it were, whereby the latter remains viable for decades in the body of the former without exerting any tissue reaction and perhaps without increasing in numbers, yet is ever ready and able to initiate an inflammatory reaction should conditions (as yet imperfectly understood) favor the development of new generations of organisms, and retains, as a parasite, the ability to infect and produce disease in a new host. This state of affairs implies a delicate adjustment between host and parasite, actually, of course, it is but another way of describing the course of syphilitic infection as observed in man. As Levaditi has pointed out, it presupposes a certain plasticity on the part of the treponemes, but there is no reason to suppose that such a condition might not be inherent in these organisms, or possibly be developed in them in response to the proper demand. Indeed the experiments of Zinsser and his co-workers make it seem entirely likely that treponemes do possess plasticity in the sense that they are capable of undergoing profound changes in both virulence and susceptibility to antagonistic agents. Attention has already been called to the experiments in which these investigators demonstrated that when *T pallidum* was cultivated in the test tube the microorganisms lost all virulence for rabbits and were readily agglutinated and underwent lysis in the serum of immunized animals whereas the same strain, while being propagated in rabbits, not only retained its virulence but was incapable of being agglutinated or dissolved by the same serum.

The hypothesis that an equilibrium is set up between host and parasite through a process of mutual immunization or adaptation, attractive as it may be, still leaves unexplained the causes for the disturbances in this equilibrium which later bring about manifestations of disease. One must assume, in accordance with this theory, that such disturbances do occur in order to account for the subsequent development of manifestations of syphilis after a period of latency. Eberson's view is that treponemicidal activity evolved by the host in response to

invasion by the treponemes is responsible for the maintenance of the latent state, but he gives no explanation for the subsidence of this activity and the attendant resumption of the disease process

When for reasons as yet obscure the balance is disturbed and new inflammatory reactions are set up with the development of macroscopic lesions, do these new lesions represent an increase in the number of treponemes or an exaltation of their virulence, or both, and is the reaction similar to that which would be exhibited by a normal individual or one in the early stages of the disease? Or is there evidence that the body of the syphilitic individual, by reason of the existence of syphilitic infection within it for some time, has been changed and now reacts in an altogether different manner? All the evidence is in favor of the latter view. Clinical and pathological experience, as is well known, shows that the tissues of the syphilitic individual, who has carried his infection for some time, react toward his own virus in a manner altogether different from that of a normal person. The character of the late lesions is markedly different from that of the early ones—destructive and proliferative changes are in the ascendancy in the case of the former, and yet it is the universal experience that treponemes are extremely scarce in tertiary lesions. The inflammatory response in late syphilis is indeed out of proportion, apparently, to the size of the stimulus, and this indication is sufficient to place the late tertiary lesions in the category of allergic phenomena. Moreover, animal inoculation has demonstrated that the organisms found in these lesions do not possess an exalted virulence, hence there is no reason to ascribe to changes in the virulence of the virus, the greater tissue response exhibited by the late lesion. Rather, on the other hand, should it be ascribed to changes in the host.<sup>9</sup>

<sup>9</sup> Bergel (130) has suggested an explanation for the difference in character between early and late lesions which emphasizes changes in the parasite rather than in the host. His view is that in the course of syphilitic infection the infecting agent is altered by reason of the defensive mechanism of the host, that this alteration is expressed in a change in the chemical constitution of the virus, and that the chemically altered virus is capable of setting up a different sort of cellular reaction from that occasioned by the unaltered virus. He thinks that the cellular picture of an inflammatory reaction is conditioned in part by the chemical nature of the antigen, that in early syphilis the reaction is primarily lymphocytic, due to the lipid nature of the (as yet) unaltered treponemes, but that later, when through the action of lipolytic enzymes the treponemes are divested of their lipid constituents, the chemical constitution of these organisms is changed and con-

treponemes and the body cells to evoke an inflammatory reaction but not enough to make this reaction overwhelming for the former. In the final analysis the difference or the similarity must be a metabolic one and perhaps we shall have to wait for a clearer understanding of the physiological processes of the treponemes and body cells as well, before light is thrown on the question. To make my meaning clear in this connection, I cannot do better than quote from Theobald Smith (159) who wrote in 1913 as follows: "There is another type of parasite which may dispense largely with both offensive and defensive processes. We can conceive of this type as exerting a metabolic activity approximating so closely to that of the host that the latter reacts but slightly, and then only after a long period of stimulation. This type of parasite would have very little that is body-foreign or blood-foreign. In this latter class I would place such organisms as the spirochete of syphilis. If the exquisite, prolonged parasitism of this microorganism, the relatively slight lesions and their curability, be borne in mind, it will be understood why I place it in this category."

#### GENERAL SUMMARY

Thus far the only animal species that have been found to be regularly susceptible to infection with *T. pallidum* are man, the monkey and the rabbit<sup>10</sup>. There is no evidence to show that any races of man are naturally insusceptible to syphilis, although some races do seem to react differently from others to the infection. Of natural individual immunity to syphilis nothing is known.

With reference to acquired immunity to syphilis, clinical experience has demonstrated that second attacks of this infection in the same individual are extremely rare. Inoculations of patients in various stages of the disease with active syphilitic virus have shown that the syphilitic individual gradually acquires a resistance against luetic virus introduced into the skin from without. This resistance is not absolute, however, but appears to be more pronounced during the later stages of the disease. Inoculation of patients presenting secondary or tertiary manifestations of syphilis with virulent syphilitic virus

<sup>10</sup> Since the above was written Kolle and Evers (163) have reported the successful transmission of syphilis to guinea pigs with such regularity, apparently, as to permit the utilization of this species for the experimental study of syphilis.

under certain circumstances leads to the development of lesions simulating those characteristic of the particular stage of syphilis in which the individual happens to be. Such inoculations very rarely lead to the production of a chancre followed by secondary manifestations, such as occurs in the ordinary evolution of the disease in a normal individual.

Experiments show that syphilitic monkeys and rabbits also acquire a resistance to a second infection. In the rabbit this resistance is first manifest about 6 to 8 weeks after inoculation and appears to be firmly established by the fifteenth week of the disease. In the monkey, also, the resistance requires time for its development. There is some experimental evidence which indicates that in the rabbit the refractory state is not equally imparted to all tissues of the body.

Neisser advanced the view that the acquired refractory state in syphilis is dependent upon the persistence of foci of syphilitic infection. Recent experimental evidence suggests that rabbits, at least, may acquire during the course of syphilis an immunity which will persist after the infection has been abolished. Treatment of syphilitic rabbits at appropriate intervals after infection is capable of arresting the development of this resistant state but not of abolishing it, once it is established. Clinical experience in respect of the occurrence of reinfections in man is not in conflict with the conception of an acquired immunity which persists in the absence of the disease. This conception, if fully substantiated, will dispose of the reinoculation test as a criterion of cure of syphilis.

Recent experiments with rabbits show that the acquired refractory state which develops in these animals during the course of syphilitic infection is more effective against a second inoculation with homologous strains than with heterologous strains. There is also evidence to show that it is possible to reinfect treated syphilitic rabbits without the development of a characteristic syphilitic lesion at the site of reinoculation. The time at which treatment is begun and the mode of reinoculation appear to be two factors which play a part in bringing about this type of reaction.

Attempts to produce in man or the lower animals, active immunity to syphilitic infection by the utilization of derivatives of syphilitic tissue, cultures of treponemes, syphilitic virus (living or dead), or



treponemes and the body cells to evoke an inflammatory reaction but not enough to make this reaction overwhelming for the former. In the final analysis the difference or the similarity must be a metabolic one and perhaps we shall have to wait for a clearer understanding of the physiological processes of the treponemes and body cells as well, before light is thrown on the question. To make my meaning clear in this connection, I cannot do better than quote from Theobald Smith (159) who wrote in 1913 as follows: "There is another type of parasite which may dispense largely with both offensive and defensive processes. We can conceive of this type as exerting a metabolic activity approximating so closely to that of the host that the latter reacts but slightly, and then only after a long period of stimulation. This type of parasite would have very little that is body-foreign or blood-foreign. In this latter class I would place such organisms as the spirochete of syphilis. If the exquisite, prolonged parasitism of this microorganism, the relatively slight lesions and their curability, be borne in mind, it will be understood why I place it in this category."

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Attempts to produce in man or the lower animals, active immunity to syphilitic infection by the utilization of derivatives of syphilitic tissue, cultures of treponemes, syphilitic virus (living or dead), or

products of the latter, have been uniformly unsuccessful, provided the disease itself was not produced. Nor have such methods had much effect upon the course of an already established infection. Attempts to confer immunity to syphilis by passive transfer of serum from immune persons or animals have likewise been fruitless. Apparently infection with virulent virus is necessary to produce immunity, although perhaps not essential to maintain it.

It has been possible to demonstrate antibodies such as agglutinins, precipitins and treponemicidal substances in the serum of animals following immunization with virus from syphilitic tissue, or more particularly with cultures, and some observers have reported the presence of these antibodies in the serum of patients with syphilis, but it is not at all clear that these substances have anything to do with natural or acquired immunity to this infection. It is significant that they have been found to be less effective against virus obtained from syphilitic lesions than against cultures of the organism.

There seems to be a biologic relationship between syphilis and yaws, although this question is by no means settled. There is as yet no evidence of any biologic relationship between *T. pallidum* and the organism causing venereal spirochetosis (*T. cuniculi*) of rabbits.

The mechanism of immunity in syphilis is not by any means clearly understood. There is on the whole little evidence that antibodies circulating in the blood are responsible for acquired resistance. The part played by the cells is not fully established although these are undoubtedly of prime importance in the resistance mechanism. It is certain that the tissues of the syphilitic individual acquire the capacity to react to new syphilitic virus introduced from without and also to the individual's own virus, in a manner wholly different from that manifested by the normal individual. This altered reaction capacity may at times manifest itself as a state of apparent indifference or anergy, again as a state of hypersusceptibility or allergy. Both of these states may be functions of the defensive process and may serve a useful purpose so far as the individual is concerned. Spontaneous sterilizing immunity in syphilis, if it ever occurs, must be extremely rare. Man seems to be incapable, as a rule, of eliminating syphilitic infection from his body unaided, although he does possess the ability to react against it and to limit somewhat its extent. This reaction

at its best is incomplete, however, although fairly effective for long periods of time. The fact that it is incomplete may be due in part to an immunization of the invading organism against the host, so that a balance is struck between the two, a mutual adjustment as it were, whereby a state of ideal parasitism is approximated, or else to some similarity between the metabolic activities of treponemes on the one hand, and the body cells on the other.

## BIBLIOGRAPHY

- (1) NEISSER, A. *Arb a d kais Gsndhtsamte*, 1911, xxxvii, 1
- (2) LEVADITI, C. *Ztschr f Immunitätsforsch u exper Therap*, 1910, II Teil, Ref 277
- (3) BRUCK, C. *Handbuch der Pathogen Mikroorganismen*, Kollé und Wassermann, Band vii, Jena, Gustav Fischer, 1913
- (4) ZINSSER, H. *Infection and Resistance*, 3rd Edition, New York, MacMillan
- (5) PLAUT, F, AND MULZER, P. *Münch med Wchnschr*, 1924, lxxi, 9
- (6) BROWN, W H, AND PEARCE, L J. *Exper Med*, 1925, xli, 795
- (7) UHLENHUTH, P, AND MULZER, P. *Arh a d k Gsndhtsamte*, 1913, xlii, 1
- (8) BROWN, W H, AND PEARCE, L J. *Exper Med*, 1925, xli, 795
- (9) ROTSCHUH, E. *Arch f Schiffs u Tropenhygiene*, 1908, xii, 109
- (10) QUENNEC. *Arch f Schiffs- u Tropenhygiene*, 1902, vi, 127
- (11) ROLLET, J. *Traité des Maladies Vénériennes*, Paris, 1865
- (12) RICORD, P. Cited by Rollet (11)
- (13) HUNTER, J. *A Treatise on the Venereal Disease*, 3rd Edition, London, 1810, pp 312-313
- (14) RICORD, P. Cited by Rollet (11)
- (15) CLERC. Cited by Rollet (11)
- (16) MAURIAC, C. *Leçons sur les Maladies Vénériennes*, Paris, 1883, p 285
- (17) TAYLOR, R W. *Journ Cut Dis*, 1890, viii, 457
- (18) PONTOPPIDAN. *Annales de Dermatol et de Syphiligr*, 2 s., 1885, v, 195
- (19) SCHNEFF. Cited by Rollet (11)
- (20) METSCHNIKOFF, E, AND ROUV, E. *Ann de l'Inst Pasteur*, 1905, xix, 673
- (21) FINGER, E, AND LANDSTEINER, K. *Archiv f Dermatol u Syph*, 1906, lxxxi, 147
- (22) KRAUS, R, AND VOLK, R. *Wien klin Wchnschr*, 1906, xix, 620
- (23) TRUFFI, M. *Zentralbl f Bakt*, 1910, liv, Orig 1 Abt, 337
- (24) NICHOLS, H J. *J Exper Med*, 1911, xiv, 196
- (25) QUEYRAT. *Annales de Dermatol et Syph*, 4 Serie, 1906, vii, 147, 292
- (25a) NOBL. *Verhandl der deutsch dermat Gesellsch*, 1906, I Teil, 270
- (26) LEVADITI, LA ROCHE AND YAMANOUCHE. *Compt rend de la soc de Biol*, 1908, lixiv, 720
- (27) FINGER, E. *Handbuch der Geschlechtskrankheiten*, Vienna, 1912, Bd ii, 942
- (28) EHLMANN. Cited by Neisser (1), also *Verhandl d deutsch dermat Gesellsch*, 1906, I Teil, 265
- (29) CAPELLI, J. *Giorn ital de dermatol e sifilol*, 1925, lxxvi, 874, cited in *Zentralbl f Haut- u Geschlechtskrhkn*, 1926, xviii, 235

- (30) METSCHNIKOFF, E Arch génér de Méd , 1905, cxcv, p 1623.
- (31) BERTARELLI, E Centralbl f Bakt , 1 Abt , Orig , 1906, xli, 320
- (32) BERTARELLI, E Centralbl f Bakt , 1 Abt , Orig , 1908, xlvI, 51.
- (33) TRUFFI, M Centralbl f. Bakt , 1 Abt , Orig , 1909, lu, 555
- (34) PURCKHAUER, R Arb a d kais Gsndhtsamte , 1911, xxxvii, 569.
- (35) COLOMBO, G L Annali di Ottalmologia, Vol 43, Nos 9, 12, cited in Derm Wchnschr , 1915, lx, 213
- (36) UHLENHUTH, P, AND WEIDANZ, O Deutsch med Wchnschr , 1908, xxxiv, 862
- (37) UHLENHUTH, P, AND MULZER, P Arbeiten a d kais Gsndhtsamte , 1913, xlv, 149
- (38) TOMASZEWski, E Berl klin Wchnschr , 1910, xlviii, 1447
- (39) ADACHI, Y . Acta Dermatologica, (Japan), 1925, v, 275
- (40) FREI, W Archiv f Derm und Syph , 1923, cxliv, 365
- (41) TRUFFI, M Centralbl. f Bakt , 1 Abt , Orig , 1909, lu, 555, and idem, 1910, lv, 337
- (42) OSSOLA Giorn ital d mal ven e d pelle, 1909, i, 171
- (43) ZINSSER, H, HOPKINS, J G, AND MCBURNEY, M J Exper Med , 1916, xxiv, 561
- (44) FOURNIER, L, AND SCHWARTZ Bull de la soc franç de Derm et de Syph , 1921, xxviii, 482
- (45) BROWN, W H , AND PEARCE, L · Proc Soc Exper Biol and Med , 1921, xviii, 255
- (46) KOLLE, W Deutsch med Wchnschr , 1922, xlviii, 1301
- (47) REITER, H Centralbl f Bakt , 1 Abt , Orig , 1924, xcii, 534
- (48) CHESNEY, A M , AND KEMP, J E J Exper Med , 1924, xxxix, 553
- (49) CHESNEY, A M , AND KEMP, J E J Exper Med , 1925, xlii, 17
- (50) ADACHI, Y Acta Dermatologica, (Japan), 1925, v, 42
- (51) KOLLE, W Deutsch med Wchnschr , 1926, lu, 11
- (52) BROWN, W H , AND PEARCE, L J. Exper Med , 1921, xxxiii, 553
- (53) In press
- (54) PEARCE, L, AND BROWN, W H Proc Soc Exper Biol and Med , 1920, xvii, 164
- (55) SALMON, P Compt rend de la soc. de Biol , 1907, lxii, 254.
- (56) QUEYRAT AND PINARD Bull de la soc franç de Derm et Syph , 1909, xx, 156.
- (57) VIGNOLO-LUTATI, K Derm Centralbl , 1912, xv, 354
- (58) VON POór, F Arch f Derm u Syph , 1913, cxvi, 379
- (59) KRAFFT-EBING Cited in Nonne, M , Syphilis and the Nervous System, Trans by Ball, C R , 2nd Ed , Philadelphia, 1916 Lippincott
- (60) SIEMENS, H W Zentralbl f d ges Neurol u Psych , 1924, xxxviii, 479
- (61) STEINER, G Arch f Psych u Nervenkrhtn , 1925, lxxiv, 457
- (62) SAGEL, W Deutsch med Wchnschr , 1926, lu, 778
- (63) JAHNEL, F Cited by Steiner, G (61).
- (64) ADACHI, Y Acta Dermatologica, (Japan), 1925, iv, 393
- (65) BROWN, W H , AND PEARCE, L J Exper Med , 1921, xxviii, 553
- (66) CHESNEY, A M , AND KEMP, J E J Exper Med , 1925, xlii, 33
- (67) NICHOLS, H J , AND WALKER, J E J Exper Med , 1923, xxxvii, 525
- (68) VOEGTLIN, C , ARMSTRONG, C , AND DYER, H Pub Health Rep , United States Public Health Service, 1923, xxxviii, 1815
- (69) CHESNEY, A M , AND KEMP, J E In press (J. Exper Med )
- (70) VOEGTLIN, C , AND DYER, H Public Health Rep , United States Public Health Service, 1925, xl, 2511

- (71) FINGER, E Cited by Neisser (1)
- (72) JACOBI, L Archives Dermatol and Syph, 1920, II, 493
- (73) PICK, W Med Klinik, 1921, XVII, 1285
- (74) BENARIO, J Die Reinfektionen bei Syphilis usw, 1914, Halle, 127 pp, C Marbold
- (75) PRIGGE, R Deutsch med Wchnschr, 1926, III, 356
- (76) BUSCHKE, A, AND KROß, H Klin Wchnschr, 1922, I, 2323
- (77) BROWN, W H, AND PEARCE, L Proc Soc Exp Biol and Med, 1921, XVIII, 255
- (78) KOLLE, W, AND EVERS, E Deutsch med Wchnschr, 1926, III, 557
- (79) AUZIAS-TURENNE Gaz Méd de Paris, 1850
- (80) DE LUCA, R, AND CASAGRANDE, O Gior ital d mal ven e d pelle, 1905, XLVI, 661
- (81) METSCHNIKOFF, E, AND ROUX, E Ann de l'Inst Pasteur, 1904, XVIII, 657
- (82) TRUFFI, M Centralbl f Bakt, 1910, I Abt, Ong, LIV, 145
- (83) SPITZER, L Wien klin Wchnschr, 1906, XIX, 1132
- (84) BRANDWEINER, A Wien klin Wchnschr, 1905, XVIII, 1176
- (85) KREIDICH, K Wien klin Wchnschr, 1906, XIX, 199
- (86) METSCHNIKOFF, E, AND ROUX, E Ann de l'Inst Pasteur, 1904, XVII, 1
- (87) GRAETZ, F, AND DELBANCO, E Med Klin, 1914, 375-420
- (88) GAHYLLE, E Compt rend de la soc de Biol, 1924, XCI, 911
- (89) NAKANO Archiv f Derm u Syph, 1913, CXVI, 265
- (90) ZINSSER, H, HOPKINS, J G, AND MCBURNEY, M J Exper Med, 1916, XXIII, 341
- (91) GROUVEN, C Deutsch med Wchnschr, 1911, XXXVII, 1647
- (92) SCHERSCHESKY, J Compt rend d l soc de Biol, 1913, LXXV, 222.
- (93) NOGUCHI, H Cited by Noguchi, H, and Akatsu, S (108)
- (94) NEISSER, A Arch f Derm u Syph, 1898, XLIV, 431
- (95) HOFFMANN, E, AND VON PROWAZEK Arb a d kais Gsndtsamte, 1911, XXXVII, 205
- (96) ZABOLOTNY, D, AND MASLAKOWETZ Centralbl f Bakt., Ong, I Abt, 1907, XLIV, 532
- (97) LANDSTEINER, K, AND MUCHA Centralbl f Bakt, I Abt, Ref 1907, XXXIX, 540
- (98) UHLENHUTH, P, AND MULZER, P Arb a d kais Gsndtsamte, 1913, XLIV, 151
- (99) TOURAINE, A Les Anticorps Syphilitiques Thèse Steinhil, Paris, 1912
- (100) KISSMEYER, A Deutsch med Wchnschr, 1915, XI, 306
- (101) KOLMER, J A, BROADWELL, S, AND MATSUNAMI, T J Exper Med, 1916, XXIV, 333
- (102) ARNHEIM, G Ztschr f Hyg u Infektionskrankh, 1914, LXXVI, 407
- (103) ZINSSER, H, HOPKINS, J G, AND MCBURNEY, M J Exper Med, 1916, XXIV, 561
- (104) SIEMENS, H W, AND BLUM, K Ztschr f Immunitätsforsch u exper Therap, 1925, XLII, 81
- (105) BLUM, K Ztschr f Immunitätsforsch u exper Therap, 1924, XI, 491
- (106) KOLMER, J A J Exper Med, 1913, XVIII, 18
- (107) ZINSSER, H, AND HOPKINS, J G J Exper Med, 1915, XXI, 576
- (108) NOGUCHI, H, AND AKATSU, S J Exper Med, 1917, XXV, 765
- (109) ZINSSER, H, HOPKINS, J G, AND MCBURNEY, M J Exper Med, 1915, XXIII, 341
- (110) ZINSSER, H, AND HOPKINS, J G J Exper Med, 1915, XXIII, 323

- (111) EBERSON, F Archives of Dermatol and Syph , 1921, iv, 490
- (112) FORNET, SCHLESCHESKY, EISENZIMMER AND ROSENFELD Deutsch med Wchnschr , 1907, xxxiii, 1679
- (113) MICHAELIS, L Berl klin Wchnschr , 1907, xlv 1477
- (114) JACOBSTHAL, E · Munch med Wchnschr , 1910, lvii, 215, also Ztschr f Immunitatsforsch u exper Therap , 1910-1911, viii, 107
- (115) BRUCK, C, AND HIDAKA, S Ztschr f Immunitatsforsch u exper Therap , 1911, viii, 476
- (116) HECHT, H Ztschr f Immunitatsforsch u exper Therap , 1915-1916, xxiv, 258
- (117) MEINICKE, E Berl klin Wchnschr , 1917, liv, 613
- (118) SACHS, H, AND GEORGI, W Med Klin , 1918, xiv, 805
- (119) DREYER, G, AND WARD, H K Lancet, 1921, cc, 956
- (120) KAHN, R L Serum Diagnosis of Syphilis by Precipitation Baltimore Williams and Wilkins Company 1925
- (121) TAKENAKA, S Acta Dermatologica, (Japan), 1925, iv, 495
- (122) SACHS, H, KLOPSTOCK, A, AND WEIL, A J Deutsch med Wchnschr , 1925, li, 589, 1017
- (123) TAKENAKA, S Acta Dermatologica, (Japan), 1924, iv, 75
- (124) WAKERLIN, G E, AND CARROLL, P H Archives Dermatol and Syph , 1925, xii, 670
- (125) KEMP, J E, CHESNEY, A M, AND POOLE, A K Bull Johns Hopkins Hosp , 1926, xxxix, 132
- (126) NICHOLS, H J J Exper Med , 1911, xiv, 196
- (127) EHLMANN, S Wien klin Wchnschr , 1906, xix, 828
- (128) LEVADITI, C Ann de l'Inst Pasteur, 1906, xx, 41
- (129) ZINSSER, H, AND HOPKINS, J G Cited in Zins ser, Infection and Resistance, 3rd Edition, New York
- (130) BERGEL, S.. Die Syphilis im Lichte neuer experimentell-biologischer und immun-therapeutischer Untersuchungen Gustav Fischer, Jena, 1925
- (131) MEIROWSKY, E Arch f Derm u Syph , 1909, xciv, 335
- (132) NICHOLAS, J, FAVRE, M, AND GAUTHIER, Cl Compt rend d l soc de Biol , 1910, lxxviii, 257.
- (133) NAKANO, H Arch f Derm u Syph , 1913, cxvi, 281
- (134) CIUFFO Gior ital d mal ven e d pelle, 1909, 170
- (135) JADASSOHN, J Arch f Derm u Syph , 1907, lxxxvi, 45.
- (136) BERTIN, E, AND LE BRUYANT, L Compt rend d l soc de Biol , 1910, lxxviii, 579
- (137) FONTANA Dermatolog Wchnschr , 1912, liv, 109
- (138) NOGUCHI, H J Exper Med , 1911, xiv, 557
- (139) SHERRICK, J. W J Amer Med Assn , 1915, lxxv, 404
- (140) CASTELLANI, A, AND CHALMERS, A J Manual of Tropical Medicine, Wood & Co, New York, 1920
- (141) CHARLOUIS, M Vierteljahresscher f Derm u Syph , 1881, viii, 431
- (142) PARHAM, J C Amer J Trop Med , 1922, ii, 341
- (143) BUTLER, C S Amer. J Trop Med , 1922, ii, 349
- (144) NEISSER, A, BAERMANN, G, AND HALBERSTADTER, L Munch med Wchnschr , 1906, lxx, 1337
- (145) HALBERSTADTER, L Arb a d kais Gsndhtsamte , 1907, xxvi, 48.
- (146) CASTELLANI, A Journ of Hygiene, 1907, vii, 558

- (147) LEVADITI, C, AND NATTAN LARIER, L Ann de l'Inst Pasteur, 1908, xxii, 260
- (148) NICHOLS, H J J Exper Med, 1911, xiv, 196
- (149) NICHOLS, H J Amer J Trop Med, 1925, v, 429
- (150) JAHNEL, F, AND LANGE, J Münch med Wchnschr, 1925, lxxii, 1452
- (151) KOLLE, W, RUPPERT, F, AND MOBUS, TH Arch f Derm u Syph, 1921, cxxxv, 260
- (152) MARIE, A, LEVADITI, C, AND BANU, G Compt rend de l'Acad de Sci, 1920, clxx, 1021
- (153) VON PROWAZEK Cited by Kraus and Volk (22)
- (154) JURGENS Cited by Kraus and Volk (22)
- (155) BROWN, W H, AND PEARCE, L Jour Am Med Assn, 1921, lxxvii, 1619
- (156) CHESNEY, A M, AND KEMP, J E J Exper Med, 1924, xli, 487
- (157) NEISSER, A Ann de Derm et de Syph, 2 s, 1884, iv, 607
- (158) McDONAGH, J E R Biology and Treatment of Venereal Diseases, 1916, Philadelphia, Lea and Febiger
- (159) SMITH, T Jour Amer Med Assn, 1913, ix, 1591
- (160) WORMS, W Deutsch med Wchnschr, 1926, lu, 785
- (161) JAUREGUI, F, AND LANCEOTTI, L Bull de l'Acad de Med, 1924, 92
- (162) JAUREGUI, F, AND LANCEOTTI, L Rev Méd latino amerc, 1924, x, 313, cited in Centralbl f Haut- und Geschlechtskrhtn, 1925, xvii, 691
- (163) KOLLE, W, AND EVERS, E Deutsch med Wchnschr, 1926, lu, 1075